

# Supporting Information

## Synthesis and Structure-Activity Relationship of Dehydrodieugenol B Neolignans against *Trypanosoma cruzi*

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## 1. General Experimental Considerations

### Solvents and Reagents

Dichloromethane, dioxane, tetrahydrofuran, and *N,N*-dimethylformamide were dried by passing through an activated alumina column under argon in a solvent dispenser. All other reagents were used as received. Cesium carbonate, copper(I) chloride and copper(I) iodide were weighed out in a glove box under nitrogen. Petrol refers to the fraction of petroleum ether which boils in the range 40-60 °C. Brine refers to a saturated aqueous solution of NaCl.

### Reactions

All reactions were carried out under an atmosphere of argon or nitrogen unless otherwise stated. Oven-dried glassware was used for reactions requiring anhydrous conditions.

### Chromatography

Thin-layer chromatography was performed on Merck aluminium-backed DC 60 F254 0.2 mm precoated plates, which were visualised with UV fluorescence and staining with potassium(VII) manganate or vanillin. Flash column chromatography was performed on MN Kieselgel 60M (particle size 40-63 µm), with the solvent system used in parentheses.

### Infrared Spectroscopy

Infrared spectra were recorded on a Bruker Tensor 27 Fourier transform spectrometer, as a thin film on a diamond ATR module.

### NMR Spectroscopy

<sup>1</sup>H NMR spectra were recorded at 200, 250, 400 or 500 MHz on Bruker DPX 200, DPX 250, DPX 400, DQX400, AVN 400, DRX500 and AVII 500 spectrometers. <sup>13</sup>C NMR spectra were recorded at 101 MHz or 125 MHz on Bruker DQX 400, AVN 400, DRX500 or ACII 500 (with <sup>13</sup>C cryoprobe) spectrometers. Chemical shifts ( $\delta_{\text{H}}$  and  $\delta_{\text{C}}$ ) are expressed in parts per million (ppm), referenced to the residual solvent peak of CDCl<sub>3</sub> (7.26 ppm). Coupling constants (J) are reported to the nearest 0.1 Hz. Spectra are assigned based on chemical shift, coupling constants, COSY, HSQC and HMBC data and / or comparison with similar compounds. Splitting patterns are described using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), sext. (sextet).

### Mass spectrometry

Low-resolution mass spectra (m/z) were performed on a Micromass LCT Premier Open Access. High resolution mass spectra were recorded under ESI or EI conditions on a Bruker MicroTOF.

### Melting Points

Melting points were obtained using a Griffin melting point apparatus and are uncorrected.

### Heating

For reactions that require heating, an oil bath was employed. The temperature was monitored via a temperature probe plugged into the stirrer plate.

## 2. General Synthetic Methods

### General Method A: MOM Protection of Phenols

A solution of phenol (1.0 eq) in  $\text{CH}_2\text{Cl}_2$  (0.2 M) was cooled to 0 °C and chloromethyl methyl ether was added (1.5 eq), followed by dropwise addition of *N,N*-diisopropyl-*N*-ethylamine (2.0 eq) and the reaction was allowed to reach room temperature. It was stirred until TLC showed consumption of phenol, after which time the reaction was transferred to a separating funnel and washed with 0.5M HCl, water, brine, and 1M aqueous NaOH, before being dried over  $\text{MgSO}_4$ , filtered, and the solvent removed *in vacuo*.

### General Method B: *Ortho*-Iodination of Protected Phenols

To a solution of protected phenol (1.0 eq) and TMEDA (1.5 eq) in anhydrous THF (0.6 M) at –78 °C was added *s*-BuLi (1.3 M in hexanes, 1.5 eq) dropwise. The resulting dark red solution was stirred at –78 °C for 3 hours, before the dropwise addition of a solution of iodine (1.5 eq) in anhydrous THF (4.5 M). After the addition of iodine was complete, the reaction was allowed to warm to room temperature over 1.5 hours, before being quenched with 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_5$  solution. The organic layer was removed, and the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with saturated aqueous  $\text{NH}_4\text{Cl}$  solution, brine, and then dried over  $\text{MgSO}_4$ , filtered, and the solvent removed *in vacuo*.

### General method C: Deprotection of MOM ethers

The methoxymethyl ether (1.0 eq) was dissolved in MeOH (0.03 M) and 2 M aqueous HCl (0.1 v/v) was added. The reaction was stirred at room temperature overnight. The reaction was brought to pH 5 by addition of 1 M aqueous NaOH. The product was then extracted with EtOAc. The organic layers were combined, dried over  $\text{MgSO}_4$ , filtered, and the solvent removed *in vacuo*.

### General method D: Optimised Biaryl Ether Formation

To a vial containing NMP (5 M *wrt* halide) and phenol (2.0 eq) was added cesium carbonate (2.0 eq), and the vial was evacuated and backfilled with nitrogen gas three times. The halide (1.0 eq), 2,2,6,6-TMHD (0.5 eq) and copper(I) chloride (0.5 eq) were added and the vial was evacuated and backfilled with nitrogen gas three times, before addition of dioxane (2.5 M *wrt* halide). The vial was then sealed and heated to 80 °C, and stirred until TLC showed consumption of the halide. After this time, the reaction was cooled to room temperature and diluted with  $\text{Et}_2\text{O}$ . The reaction mixture was filtered through celite, and the filter cake washed with  $\text{Et}_2\text{O}$ . The filtrate was washed with water, 1 M NaOH solution, 20% aqueous  $\text{NH}_3$  solution, and brine, and the organic layer was dried over  $\text{MgSO}_4$ , filtered, and the solvent removed *in vacuo*.

### General method E: Allylation of Phenols

To a solution of phenol (1.0 eq) in DMF (1 M) was added potassium carbonate (2.5 eq), followed by allyl bromide (1.5 eq) and the reaction heated to 50 °C and stirred for 3 h. The reaction was then cooled to rt, diluted with EtOAc and then washed with water, and the organic layer was dried over  $\text{MgSO}_4$ , filtered, and the solvent removed *in vacuo*.

#### **General method F: Methylation of Phenols**

To a solution of phenol (1.0 eq) in DMF (0.7 M) was added potassium carbonate (4.0 eq), followed by dropwise addition of methyl iodide (1.4 eq). The reaction was stirred at room temperature overnight, before being diluted with EtOAc, and washed with water and 1 M NaOH. The organic layer was dried over MgSO<sub>4</sub>, filtered, and the solvent removed *in vacuo*.

#### **General method G: PMB Protection of Phenols**

To a flask containing a solution of phenol (1.0 eq) in DMF (0.13 M) was added potassium carbonate (2.5 eq). *Para*-methoxybenzyl chloride (1.2 eq) was added dropwise with vigorous stirring. The reaction was heated to 100 °C and stirred for two hours, or until TLC showed consumption of the phenol, after which time the reaction was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was washed with water and then brine, dried over MgSO<sub>4</sub>, filtered, and the solvent removed *in vacuo*.

#### **General method H: Deprotection of PMB ethers**

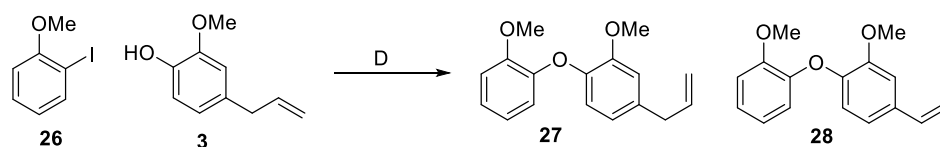
To a flask containing a solution of PMB-protected phenol (1.0 eq) in ethanol (0.05 M) was added 1 M aqueous HCl (0.5 v/v) and the reaction was heated to 80 °C until TLC showed consumption of the protected phenol, after which time the reaction was cooled to room temperature, and partitioned between water and ethyl acetate. The product was extracted with ethyl acetate and the combined organic layers were washed with brine, then dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*.

#### **General method I: Hydrogenation of Alkenes**

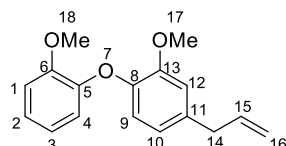
A flask containing a suspension of Pd/C (10% w/w, 0.3 eq) in ethanol (0.06 M) was evacuated of air and flushed with hydrogen (balloon) three times. The suspension was stirred vigorously under the hydrogen atmosphere for 15 minutes, before addition of the alkene (1.0 eq). The reaction was stirred under hydrogen until TLC showed consumption of the starting material. The mixture was then filtered through a pad of celite, and the filtrate dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*.

### 3. Synthesis and Characterization of Compounds

#### Optimization of cross-coupling: Manuscript Table 1

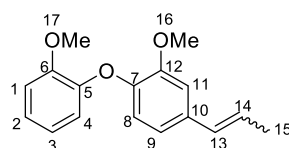


#### 4-Allyl-2-methoxy-1-(2-methoxyphenoxy)benzene, 27



**27** was prepared according to general method D using 2-iodoanisole, **26** (130  $\mu\text{L}$ , 1.0 mmol, 1.0 eq), eugenol (**3**, 308  $\mu\text{L}$ , 2.0 mmol, 2.0 eq), copper(I) chloride (99 mg, 0.5 mmol, 0.5 eq), TMHD (104  $\mu\text{L}$ , 0.5 mmol, 0.5 eq), cesium carbonate (652 mg, 2.0 mmol, 2.0 eq), NMP (0.6 mL) and dioxane (1.2 mL). The reaction was complete after 2 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0  $\rightarrow$  9 : 1), to afford 4-allyl-2-methoxy-1-(2-methoxyphenoxy)benzene, **27** (232 mg, 0.86 mmol, 86%) as an off-white waxy solid;  $R_f$  0.19 (petrol / EtOAc (9 : 1)); IR (thin film,  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$ ) 3008, 2963, 2939, 2836, 1639, 1589, 1499, 1465, 1453, 1250, 1214, 1176, 1128, 1029;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.04 (ddd,  $J = 8.1, 7.3, 1.7$  Hz, 1H, H2), 6.97 (dd,  $J = 8.1, 1.7$  Hz, 1H, H1), 6.85 (ddd,  $J = 8.1, 7.3, 1.7$  Hz, 1H, H3), 6.82–6.75 (m, 3H, H4, H9, H12), 6.69 (dd,  $J = 8.1, 2.0$  Hz, 1H, H10), 5.99 (ddt,  $J = 16.8, 10.0, 6.7$  Hz, 1H, H15), 5.17–5.04 (m, 2H, H16), 3.87 (s, 3H, H17), 3.84 (s, 3H, H18), 3.37 (dt,  $J = 6.7, 1.4$  Hz, 2H, H14);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  150.6, 150.4, 146.5, 144.0, 137.5, 136.1, 123.6, 120.9, 120.8, 119.2, 118.3, 116.0, 113.0, 112.5, 56.1, 56.0, 40.1; HRMS (EI $^+$ ) calc. for  $\text{C}_{17}\text{H}_{18}\text{O}_3$  [M] $^+$  270.1256, found 270.1257.

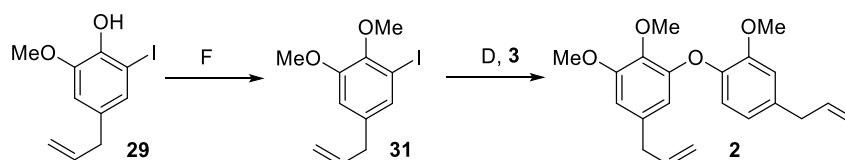
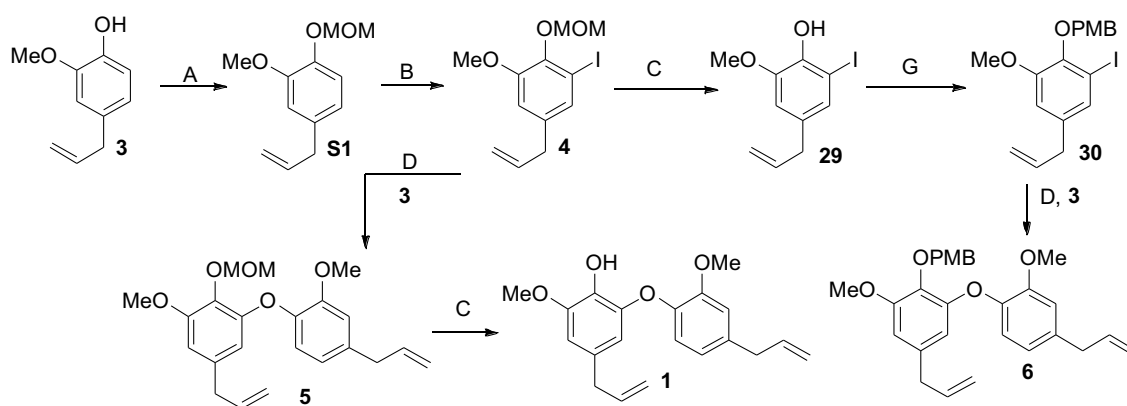
#### 2-Methoxy-1-(2-methoxyphenoxy)-4-(prop-1-en-1-yl)benzene, 28



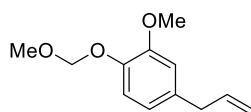
**28** was synthesised according to a modified literature procedure.<sup>1</sup> To a vial containing NMP (1.7 mL) and eugenol (**3**, 308  $\mu\text{L}$ , 2.0 mmol, 2.0 eq) was added cesium carbonate (652 mg, 2.0 mmol, 2.0 eq), and the vial was evacuated and backfilled with nitrogen gas three times. 2-Bromoanisole (125  $\mu\text{L}$ , 1.0 mmol, 1.0 eq), TMHD (21  $\mu\text{L}$ , 0.1 mmol, 0.1 eq) and copper(I) chloride (50 mg, 0.5 mmol, 0.5 eq) were added and the vial was evacuated and backfilled with nitrogen gas three times. The vial was then sealed and heated to 120  $^{\circ}\text{C}$  and stirred for two days. The reaction was cooled to room temperature and diluted with  $\text{Et}_2\text{O}$  (2 mL). The reaction mixture was filtered through celite, and the filter cake washed with  $\text{Et}_2\text{O}$  ( $3 \times 2$  mL). The filtrate was washed with water (10 mL), 1 M NaOH solution ( $3 \times 10$  mL), brine (10 mL), and the organic layer dried ( $\text{MgSO}_4$ ), filtered, and the solvent removed *in vacuo*. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0  $\rightarrow$  9 : 1), to afford **28** (68 mg, 0.25 mmol, 25%, *cis* / *trans* (1 : 0.3)) as an off-white waxy solid;  $R_f$  0.19 (petrol /

EtOAc (9 : 1)); IR (thin film,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ): 3006, 2935, 2836, 2360, 186, 1499, 1455, 1300, 1252, 1216, 1176, 1126, 1113, 1030;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.16–6.64 (m, 7H, H1, H2, H3, H4, H8, H9, H111), 6.37 (d,  $J$  = 15.5 Hz, 1H, H13), 6.17 (dq,  $J$  = 15.5, 6.5 Hz, 1H, H14 *trans*), 5.76 (dq,  $J$  = 14.1, 7.2 Hz, 0.3H H14 *cis*), 3.86 (m, 6H, H16, H17), 1.93 (d,  $J$  = 7.2 Hz, 1H H16 *cis*), 1.88 (d,  $J$  = 6.3 Hz, 2H, H16 *trans*);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , some peaks overlapping due to E/Z mixtures)  $\delta_{\text{C}}$  150.5, 150.4, 150.0, 146.1, 146.0, 144.9, 144.6, 134.1, 133.5, 130.6, 129.5, 126.2, 124.9, 123.9, 123.7, 121.4, 120.9, 118.9, 118.9, 118.6, 118.3, 113.2, 112.5, 112.5, 109.7, 55.9, 29.8, 18.5, 14.8; HRMS (ESI+) calc. for  $\text{C}_{17}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$  271.1329, found 270.1329.

### Synthesis of natural products **1** and **2**, and analogues **5,6** and **10**

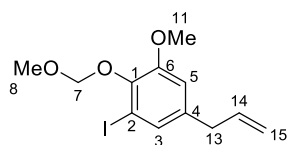


#### 4-Allyl-2-methoxy-1-(methoxymethoxy)benzene, **S1**



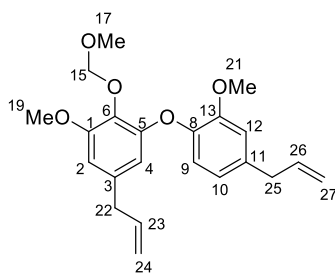
**S1** was prepared according to general method A, using eugenol (**3**, 2.2 mL, 14.4 mmol, 1.0 eq), chloromethyl methyl ether (1.6 mL, 21.6 mmol, 1.5 eq), DIPEA (5.0 mL, 28.8 mmol, 2.0 eq) and  $\text{CH}_2\text{Cl}_2$  (100 mL). The reaction was complete after 18 hours to afford on work-up **S1** (2.97 g, 14.3 mmol, 99 %) as an orange oil, which was used without further purification;  $R_f$  0.47 (petrol / EtOAc (4 : 1));  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.07 (d,  $J$  = 8.0 Hz, 1H), 6.75–6.68 (m, 2H), 5.95 (ddt,  $J$  = 16.9, 10.0, 6.7 Hz, 1H), 5.20 (s, 2H), 5.12–5.04 (m, 2H), 3.87 (s, 3H), 3.51 (s, 3H), 3.36–3.32 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  149.8, 144.8, 137.6, 134.6, 120.7, 116.7, 115.8, 112.3, 95.7, 56.2, 55.9, 40.0; HRMS (EI+) calc. for  $\text{C}_{12}\text{H}_{16}\text{O}_3$   $[\text{M}]^+$  208.1099, found 208.1094. Experimental data is in good agreement with that described in the literature.<sup>2</sup>

#### 5-Allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene, **4**



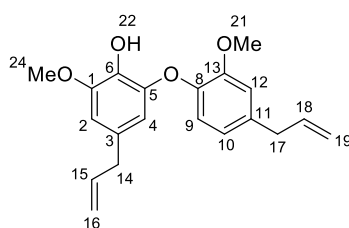
The product was prepared according to general method B, using 4-allyl-2-methoxy-1-(methoxymethoxy)benzene (**S1**, 1.26 g, 6.05 mmol, 1.0 eq), TMEDA (1.36 mL, 9.07 mmol, 1.5 eq), *s*-BuLi (1.3 M in hexanes, 1.15 mL, 1.5 mmol, 1.5 eq), iodine (2.3 g, 9.07 mmol, 1.5 eq) and THF (10 + 2 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 → 19 : 1)) to afford **4** (1.31 g, 3.92 mmol, 65%) as a colourless oil;  $R_f$  0.24 (petrol / EtOAc (9 : 1)); IR (thin film,  $\nu_{\max}/\text{cm}^{-1}$ ) 3078, 2963, 2824, 1561, 1480, 1461, 1411, 1314, 1158, 1139, 1076, 1041;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.20 (d,  $J = 1.9$  Hz, 1H, H3), 6.70 (d,  $J = 1.8$  Hz, 1H, H5), 5.97–5.84 (m, 1H, H14), 5.13 (s, 2H, H7), 5.13–5.06 (m, 2H, H15), 3.81 (s, 3H, H8), 3.67 (s, 3H, H11), 3.30 (d,  $J = 6.8$  Hz 2H, H13);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  152.2, 144.2, 138.3, 136.7, 130.8, 116.6, 113.4, 98.8, 92.7, 58.5, 56.0, 39.5; HRMS (ES+) calc. for  $\text{C}_{12}\text{H}_{15}\text{IO}_3\text{Na}$   $[\text{M}+\text{Na}]^+$  356.9958, found 356.9956.

#### 5-Allyl-1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-(methoxymethoxy)benzene, **5**



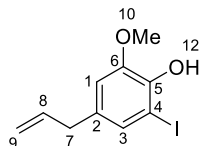
**5** was prepared according to general method D, using 5-allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene (**4**, 100 mg, 0.3 mmol, 1.0 eq), eugenol (**3**, 92  $\mu\text{L}$ , 0.6 mmol, 2.0 eq), copper(I) chloride (15 mg, 0.15 mmol, 0.5 eq), TMHD (31  $\mu\text{L}$ , 0.15 mmol, 0.5 eq), cesium carbonate (195 mg, 0.6 mmol, 2.0 eq), NMP (0.17 mL) and dioxane (0.33 mL). The reaction was complete after 2 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 → 9 : 1)) to afford **5** (34 mg, 0.09 mmol, 31%) as a pale yellow oil;  $R_f$  0.16 (petrol / EtOAc (9 : 1)); IR (thin film,  $\nu_{\max}/\text{cm}^{-1}$ ) 3078, 3072, 2839, 1639, 1606, 1505, 1466, 1452, 1333, 1265, 1233, 1213, 1156, 1130, 1035;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.82 (d,  $J = 8.1$  Hz, 1H, H9), 6.79 (d,  $J = 2.0$  Hz, 1H, H12), 6.70 (ddt,  $J = 8.1, 1.9, 0.6$  Hz, 1H, H2), 6.49 (d,  $J = 1.9$  Hz, 1H, H2), 6.27–6.24 (m, 1H, H26), 5.98 (ddt,  $J = 16.8, 10.1, 6.7$  Hz, 1H, H26), 5.92–5.80 (m, 1H, H23), 5.17 (s, 2H, H15), 5.14–5.00 (m, 4H, H24, H27), 3.86 (s, 3H, H19), 3.82 (s, 3H, H21), 3.57 (s, 3H, H17), 3.37 (dt,  $J = 6.8, 1.5$  Hz, 2H, H22), 3.23 (dt,  $J = 6.6, 1.4$  Hz, 2H, H25);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  153.7, 150.9, 150.7, 143.9, 137.5, 137.2, 136.2, 136.2, 134.5, 120.9, 119.7, 116.0, 116.0, 113.1, 111.2, 107.3, 98.5, 57.2, 56.1, 56.0, 40.2, 40.1; HRMS (ES+) calc. for  $\text{C}_{22}\text{H}_{27}\text{O}_5$   $[\text{M}+\text{H}]^+$  371.1853, found 371.1850.

## Dehydrodieugenol B, **1**



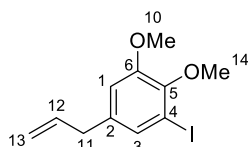
**1** was prepared according to general method C, using 5-allyl-1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-(methoxymethoxy)benzene (**5**, 28 mg, 0.08 mmol, 1.0 eq), 2 M aqueous HCl (0.25 mL), and methanol (2.5 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (9 : 1 → 7 : 3) to give dihydrodieugenol **1** (13 mg, 0.04 mmol, 52%) as a yellow oil;  $R_f$  0.28 (petrol / EtOAc (7 : 3)); IR (thin film,  $\nu_{\max}$ /  $\text{cm}^{-1}$ ) 3674, 2980, 2886, 2360, 2340, 1639, 1509, 1312, 1152, 1129, 1086, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.89 (d,  $J$  = 8.1 Hz, 1H, H9), 6.80 (d,  $J$  = 1.9 Hz, 1H, H12), 6.73–6.68 (m, 1H, H10), 6.49 (d,  $J$  = 1.8 Hz, 1H, H2), 6.42–6.38 (m, 1H, H4), 6.06–5.85 (m, 2H, H15, H18), 5.84 (s, 1H, H22), 5.15–4.98 (m, 4H, H16, H19), 3.89 (s, 3H, H24), 3.86 (s, 3H, H21), 3.37 (dt,  $J$  = 6.7, 1.5 Hz, 2H, H17), 3.24 (dt,  $J$  = 6.7, 1.5 Hz, 2H, H14);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  150.5, 148.0, 144.3, 144.3, 137.6, 137.4, 136.6, 135.3, 131.2, 121.0, 119.6, 116.1, 115.9, 113.0, 112.0, 107.4, 56.4, 56.1, 40.1, 40.1; HRMS (ESI+) calc. for  $\text{C}_{20}\text{H}_{22}\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$  349.1410, found 349.1410. Experimental data is in good agreement with that described in the literature for the isolated natural product.<sup>3</sup>

## 4-Allyl-2-iodo-6-methoxyphenol, **29**



**29** was prepared according to general method C using 5-allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene (**4**, 1.3 g, 3.9 mmol, 1.0 eq), 1 M aqueous HCl (10 mL) and MeOH (100 mL) was added 1 M aqueous HCl (10 mL). The reaction was complete after 18 hours to afford **29** (987 mg, 3.4 mmol, 87% crude) as a pale yellow waxy solid, which was used without further purification. A sample was purified for analysis *via* flash column chromatography (petrol / EtOAc (1 : 0 → 4 : 1) to afford a colourless wax;  $R_f$  0.37 (petrol / EtOAc (4 : 1)); IR (thin film,  $\nu_{\max}$ /  $\text{cm}^{-1}$ ); 3077, 2916, 2849, 2361, 1581, 1492, 1462, 1419, 1361, 1274, 1176, 1139, 1043;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.12 (s, 1H, H1), 6.65 (s, 1H, H3), 5.96 (s, 1H, H12), 5.95–5.84 (m, 1H, H8), 5.12–5.04 (m, 2H, H9), 3.87 (s, 3H, H10), 3.28 (d,  $J$  = 6.6 Hz, 2H, H7);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  145.9, 144.0, 137.1, 133.7, 130.1, 116.2, 111.3, 81.2, 56.2, 39.4; HRMS (ES-) calc. for  $\text{C}_{10}\text{H}_{10}\text{IO}_2$  [ $\text{M}-\text{H}$ ] $^-$  288.9725, found 288.9715.

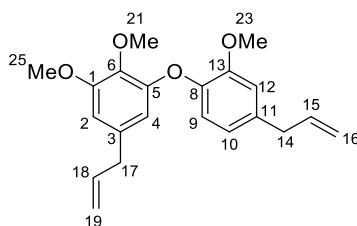
## 5-Allyl-1-iodo-2,3-dimethoxybenzene, **31**



**31** was prepared according to general method F using 4-allyl-2-iodo-6-methoxyphenol (**29**, 443 mg, 1.52 mmol, 1.0 eq), methyl iodide (133  $\mu\text{L}$ , 2.13 mmol, 1.4 eq), potassium carbonate (842 mg, 6.09

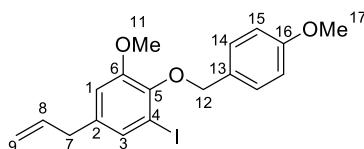
mmol, 4.0 eq), and DMF (2.2 mL). The crude residue was purified *via* flash column chromatography (petrol / Et<sub>2</sub>O (19 : 1)) to afford **31** (309 mg, 1.0 mmol, 67%) as a colourless oil; R<sub>f</sub> 0.51 (petrol / EtOAc (9 : 1)); IR (neat, ν<sub>max</sub>/ cm<sup>-1</sup>) 2933, 1638, 1590, 1560, 1481, 1462, 1425, 1408, 1267, 1234, 1180, 1139, 1043, 1000; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.17 (d, *J* = 1.9 Hz, 1H, H1), 6.70 (d, *J* = 1.9 Hz, 1H, H3), 5.91 (ddt, *J* = 16.1, 10.9, 7.1 Hz, 1H, H12), 5.14–5.05 (m, 2H, H13), 3.84 (s, 3H, H10), 3.80 (s, 3H, H14), 3.29 (dt, *J* = 7.1, 1.6 Hz, 2H, H11); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 152.5, 147.3, 138.2, 136.7, 130.2, 116.5, 113.3, 92.4, 60.5, 56.0, 39.5; HRMS (Methane CI) calc. for C<sub>11</sub>H<sub>14</sub>O<sub>2</sub> [M+H]<sup>+</sup> 305.0033, found 305.0033.

### 5-Allyl-1-(4-allyl-2-methoxyphenoxy)-2,3-dimethoxybenzene, **2**



**2** was prepared according to general method D, using 5-allyl-1-iodo-2,3-dimethoxybenzene (**31**, 152 mg, 0.5 mmol, 1.0 eq), eugenol (**3**, 154 μL, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52 μL, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after 3 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 → 9 : 1)), to afford **2** (99 mg, 0.29 mmol, 58%) as a colourless oil; R<sub>f</sub> 0.24 (petrol / EtOAc (9 : 1)); IR (thin film, ν<sub>max</sub>/ cm<sup>-1</sup>) 2920, 2850, 2361, 1638, 1587, 1507, 1452, 1426, 1332, 1266, 1233, 1213, 1153, 1130, 1093, 1036; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 6.85–6.78 (m, 2H, H9, H12), 6.69 (dd, *J* = 8.2, 1.9 Hz, 1H, H10), 6.48 (d, *J* = 1.9 Hz, 1H, H2), 6.27 (d, *J* = 1.9 Hz, 1H, H4), 6.04–5.82 (m, 2H, H15, H18), 5.15–4.97 (m, 4H, H16, H19), 3.87 (s, 6H, H25, H21), 3.83 (s, 3H, H23), 3.37 (d, *J* = 6.7 Hz, 2H, H14), 3.24 (d, *J* = 6.6 Hz, 2H, H17); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 153.6, 150.7, 144.3, 138.2, 137.5, 137.2, 136.1, 135.7, 120.9, 119.6, 116.0, 116.0, 113.2, 111.5, 107.4, 61.2, 56.2, 56.0, 40.2, 40.1; HRMS (ESI<sup>+</sup>) calc. for C<sub>21</sub>H<sub>24</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup> 363.1572, found 363.1572. Experimental data is in good agreement with that described in the literature for the isolated natural product.<sup>3</sup>

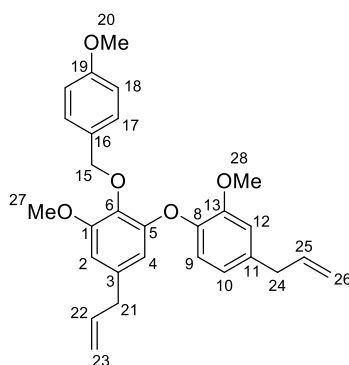
### 5-Allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **30**



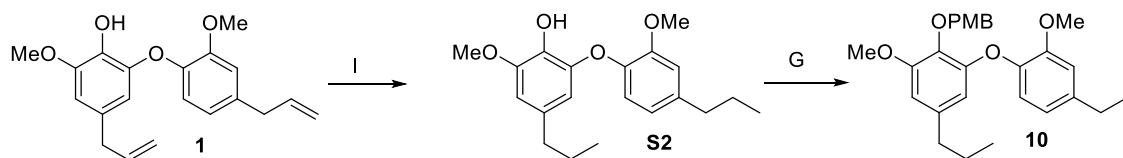
**30** was prepared according to general method H, using 4-allyl-2-iodo-6-methoxyphenol, **29** (500 mg, 1.72 mmol, 1.00 eq), *para*-methoxybenzyl chloride (280 μL, 2.07 mmol, 1.20 eq), potassium carbonate (596 mg, 4.31, mmol, 2.5 eq) and DMF (13 mL). The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0 → 19 : 1)) to afford **30** (570mg, 1.39 mmol, 81%) as a colourless oil; R<sub>f</sub> 0.53 (petrol / EtOAc (9 : 1)); IR (neat, ν<sub>max</sub> / cm<sup>-1</sup>) 2934, 2835, 1638, 1612, 1513, 1461, 1409, 1372, 1266, 1248, 1227, 1173, 1141, 1039; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.50 (d, *J* = 8.3 Hz, 2H, H14), 7.19 (d, *J* = 1.9 Hz, 1H, H1), 6.94 – 6.89 (m, 2H, H15), 6.71 (d, *J* = 1.7 Hz, 1H, H3), 5.93 (dddd, *J* = 19.1, 9.6, 7.4, 6.2 Hz, 1H, H8), 5.14 – 5.07 (m, 2H, H9), 4.91 (s, 2H, H12), 3.85 (s, 3H, H17), 3.82 (s, 3H, H11),

3.31 (d,  $J = 6.7$  Hz, 2H, H7);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.6, 152.7, 146.2, 138.2, 136.8, 130.5, 130.4, 129.5, 116.6, 113.8, 113.4, 93.2, 74.4, 56.1, 55.4, 39.6; HRMS (APCI) calc. for  $\text{C}_{18}\text{H}_{20}\text{O}_3$   $[\text{M}+\text{H}]^+$  411.0452, found 446.0450.

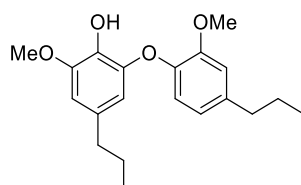
### 5-Allyl-1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, 6



**6** was prepared according to general method D, using 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene (**30**, 1.23 g, 3.0 mmol, 1.0 eq), eugenol (**3**, 921  $\mu\text{L}$ , 6.0 mmol, 2.0 eq), copper(I) chloride (148 mg, 1.5 mmol, 0.5 eq), TMHD (312  $\mu\text{L}$ , 1.5 mmol, 0.5 eq), cesium carbonate (1.95 mg, 6.0 mmol, 2.0 eq), NMP (2.0 mL) and dioxane (4.0 mL). The reaction was complete after 3 days. The crude residue was purified *via* flash column chromatography (petrol : EtOAc (1 : 0  $\rightarrow$  4 : 1)) to afford **6** (765 mg, 1.78 mmol, 59%) as a pale yellow oil;  $R_f$  0.21 (petrol / EtOAc (9 : 1)); IR (neat,  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$ ) 3002, 2837, 1610, 1506, 1462, 1452, 1374, 1231, 1212, 1151, 1090, 1034;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.34 – 7.26 (m, 2H, H18), 6.84 – 6.77 (m, 3H, H9, H17), 6.74 (dd,  $J = 8.1, 1.6$  Hz, 1H, H10), 6.67 (s, 1H, H12), 6.48 (d,  $J = 1.9$  Hz, 1H, H2), 6.31 (d,  $J = 1.8$  Hz, 1H, H4), 6.07 – 5.81 (m, 2H, H22, H25), 5.15 – 4.99 (m, 4H, H23, H26), 4.97 (s, 2H, H15), 3.82 (m, 6H, H20, H28), 3.78 (d,  $J = 1.6$  Hz, 3H, H27), 3.37 (d,  $J = 6.8$  Hz, 2H, H21), 3.24 (d,  $J = 6.6$  Hz, 2H, H24);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.3, 154.0, 150.8, 150.5, 144.5, 137.6, 137.3, 137.1, 135.8, 135.8, 130.3, 130.2, 120.9, 119.2, 116.0, 116.0, 113.5, 113.1, 111.8, 107.7, 74.8, 56.2, 56.1, 55.4, 40.2, 40.1; HRMS (APCI) calc. for  $\text{C}_{28}\text{H}_{31}\text{O}_5$   $[\text{M}+\text{H}]^+$  447.2166, found 447.2164.



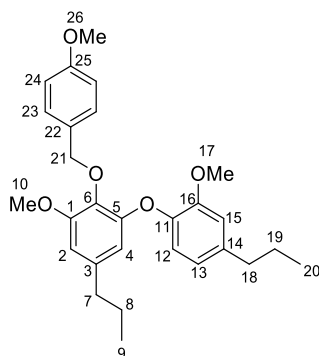
### 2-Methoxy-6-(2-methoxy-4-propylphenoxy)-4-propylphenol, S2



**S2** was prepared according to General method I, using dehydrodieugenol B (**1**, 50 mg, 0.15 mmol, 1.0 eq), hydrogen (balloon), Pd/C (10% w/w, 5.0 mmol, 0.05 mmol, 0.3 eq) and ethanol (2.5 mL). The

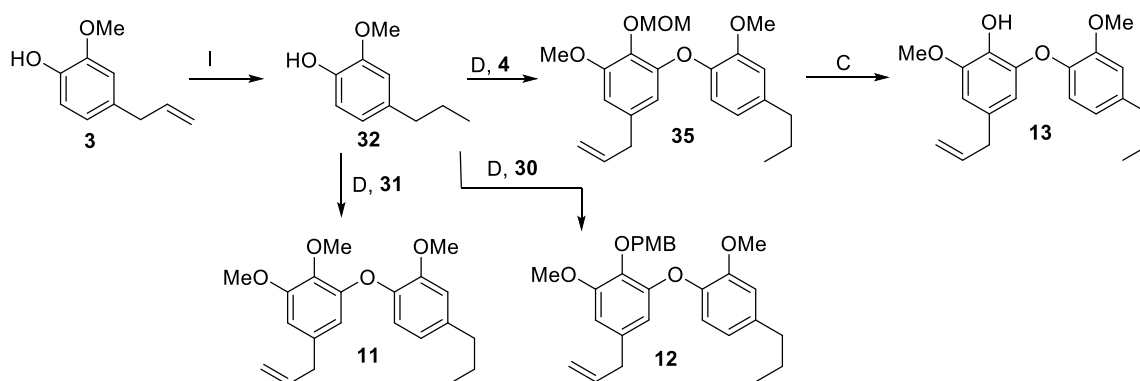
reaction was complete after one hour to afford **S2** (51 mg, 0.15 mmol, >99%) as a colourless oil;  $R_f$  0.31 (pentane / ethyl acetate (4 : 1));  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.87 (d,  $J = 8.1$  Hz, 1H), 6.79 (d,  $J = 1.9$  Hz, 1H), 6.69 (dd,  $J = 8.1, 2.0$  Hz, 1H), 6.49 (d,  $J = 1.8$  Hz, 1H), 6.40 (d,  $J = 1.8$  Hz, 1H), 5.85 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.56 (dd,  $J = 8.6, 6.7$  Hz, 2H), 2.44 (dd,  $J = 8.6, 6.7$  Hz, 2H), 1.64 (sext,  $J = 7.2$  Hz, 2H), 1.55 (sext,  $J = 7.6$  Hz, 2H), 0.95 (t,  $J = 7.3$  Hz, 3H), 0.89 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  150.3, 147.8, 144.5, 144.0, 139.2, 135.0, 133.9, 120.8, 119.9, 112.9, 111.8, 107.3, 56.3, 56.1, 38.0, 38.0, 24.8, 24.8, 14.0, 13.8; LRMS (ESI+) calc. for  $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$   $[\text{M}+\text{Na}]^+$  353.2, found 353.2. The experimental data is in good agreement with that described in the literature.<sup>4</sup>

### 1-Methoxy-3-(2-methoxy-4-propylphenoxy)-2-((4-methoxybenzyl)oxy)-5-propylbenzene, **10**

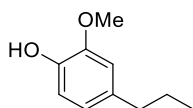


**10** was prepared according to general method E, using 2-methoxy-6-(2-methoxy-4-propylphenoxy)-4-propylphenol (**S2**, 50 mg, 0.15 mmol, 1.0 eq), *para*-methoxybenzyl chloride (25  $\mu\text{L}$ , 0.18 mmol, 1.3 eq), potassium carbonate (53 mg, 0.38 mmol, 2.5 eq) and DMF (1.3 mL). The reaction was complete after two hours. The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0  $\rightarrow$  9 : 1)) to afford 1-methoxy-3-(2-methoxy-4-propylphenoxy)-2-((4-methoxybenzyl)oxy)-5-propylbenzene, **10** (53 mg, 0.12 mmol, 77%) as a white solid; MP 56-59  $^{\circ}\text{C}$ ;  $R_f$  0.69 (pentane / ethyl acetate (4 : 1)); IR (neat,  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$ ) 2957, 2860, 1607, 1505, 1437, 1376, 1298, 1220, 1173, 1077;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.34 – 7.27 (m, 2H, H23), 6.82 – 6.79 (m, 2H, H24), 6.78 (d,  $J = 1.9$  Hz, 1H, H15), 6.73 (d,  $J = 8.2$  Hz, 2H, H12), 6.66 (dd,  $J = 8.1, 1.9$  Hz, 1H, H13), 6.47 (d,  $J = 1.9$  Hz, 1H, H2), 6.31 (d,  $J = 1.9$  Hz, 1H, H4), 4.97 (s, 2H, H21), 3.82 (s, 6H, H17, H26), 3.78 (s, 3H, H10), 2.56 (dd,  $J = 8.6, 6.7$  Hz, 2H, H18), 2.45 (dd,  $J = 8.6, 6.7$  Hz, 2H, H7), 1.65 (sext,  $J = 7.3$  Hz, 2H, H19), 1.55 (sext,  $J = 7.4$  Hz, 2H, H8), 0.96 (t,  $J = 7.3$  Hz, 3H, H20), 0.89 (t,  $J = 7.3$  Hz, 3H, H9);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.3, 153.8, 150.6, 150.3, 144.3, 138.5, 138.5, 136.4, 130.4, 130.2, 120.7, 118.9, 113.5, 113.1, 111.7, 107.6, 74.8, 56.2, 56.1, 55.4, 38.2, 38.0, 24.8, 24.6, 14.0, 13.9; HRMS (ESI+) calc. for  $\text{C}_{28}\text{H}_{35}\text{O}_5$   $[\text{M}+\text{H}]^+$  451.2479, found 451.2479.

## Synthesis of analogues **11-25**

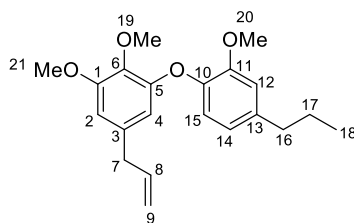


## 2-Methoxy-4-propylphenol, **32**



**32** was prepared according to general method I, using eugenol (**3**, 770  $\mu\text{L}$ , 5.00 mmol, 1.00 eq), Pd/C (10% w/w, 1.60 g, 1.50 mmol, 0.30 eq) and ethanol (75 mL). The reaction was complete after 90 minutes to afford **32** (775 mg, 4.67 mmol, 93%) as a pale yellow oil which was used without further purification;  $R_f$  0.36 (petrol / EtOAc (9 : 1));  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.84 (d,  $J = 7.8$  Hz, 1H), 6.71 – 6.65 (m, 2H), 5.48 (dd,  $J = 5.5, 1.6$  Hz, 1H), 3.88 (s, 3H), 2.52 (t,  $J = 7.4$  Hz, 2H), 1.62 (sext,  $J = 7.4$  Hz, 2H), 0.94 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  146.4, 143.6, 134.8, 121.1, 114.2, 111.1, 56.0, 37.9, 25.0, 14.0; HRMS (APCI) calc. for  $\text{C}_{10}\text{H}_{13}\text{O}_2$  [ $\text{M}-\text{H}$ ] $^-$  165.0921, found 165.0917. The experimental data is in good agreement with that described in the literature.<sup>5</sup>

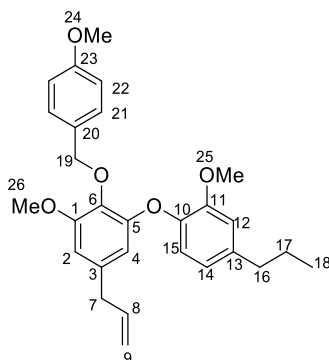
## 5-Allyl-1,2-dimethoxy-3-(2-methoxy-4-propylphenoxy)benzene, **11**



**11** was prepared according to general method D, using 5-allyl-1-iodo-2,3-dimethoxybenzene (**31**, 152 mg, 0.50 mmol, 1.0 eq), 2-methoxy-4-propylphenol (**32**, 166 mg, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52  $\mu\text{L}$ , 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified by flash column chromatography (petrol / ethyl acetate (1 : 0  $\rightarrow$  4 : 1)) to afford **11** (117 mg, 0.34 mmol, 68%) as a pale yellow oil;  $R_f$  0.30 (petrol / ethyl acetate (9 : 1)); IR (neat,  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$ ) 2958, 2933, 1586, 1452, 1423, 1333, 1265, 1154, 1129, 1091;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.84 – 6.79 (m, 2H, H15, H12), 6.71 (dd,  $J = 8.1, 1.9$  Hz, 1H, H14), 6.50 (d,  $J = 1.9$  Hz, 1H, H2), 6.29 (d,  $J = 1.9$  Hz, 1H, H4), 5.90 (ddt,  $J = 16.0, 10.7, 6.7$  Hz, 1H, H8), 5.10 – 5.00 (m, 2H, H9), 3.90 (s, 3H, H20), 3.89 (s,

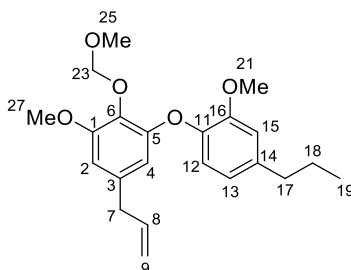
3H, H19), 3.86 (s, 3H, H21), 3.26 (dt,  $J = 6.7, 1.5$  Hz, 2H, H7), 2.59 (dd,  $J = 8.6, 6.7$  Hz, 2H, H16), 1.73 – 1.62 (m, 2H, H17), 0.98 (t,  $J = 7.3$  Hz, 3H, H18);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  153.5, 150.8, 150.5, 143.7, 138.8, 138.0, 137.1, 135.5, 120.6, 119.4, 115.9, 113.0, 111.3, 107.2, 61.0, 56.1, 56.0, 40.1, 37.9, 24.6, 13.8; HRMS (ESI+) calc. for  $\text{C}_{21}\text{H}_{27}\text{O}_4$   $[\text{M}+\text{H}]^+$  343.1904, found 343.1900.

### 5-Allyl-1-methoxy-3-(2-methoxy-4-propylphenoxy)-2-((4-methoxybenzyl)oxy)benzene, **12**



**12** was prepared according to general method D using 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene (**30**, 205 mg, 0.5 mmol, 1.0 eq), 2-methoxy-4-propylphenol (**32**, 166 mg, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52  $\mu\text{L}$ , 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after three days. The crude residue was purified by flash column chromatography (petrol / ethyl acetate (1 : 0  $\rightarrow$  4 : 1)) to afford **12** (100 mg, 0.22 mmol, 45%) as a colourless oil;  $R_f$  0.23 (pentane / diethyl ether (4 : 1)); IR (neat,  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$ ) 2957, 2933, 2360, 1587, 1511, 1463, 1375, 1265, 1232, 1155;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 – 7.27 (m, 2H, H21), 6.83 – 6.79 (m, 2H, H22), 6.78 (d,  $J = 2.0$  Hz, 1H, H12), 6.74 (d,  $J = 8.1$  Hz, 2H, H15), 6.66 (dd,  $J = 8.2, 1.9$  Hz, 1H, H14), 6.47 (d,  $J = 1.9$  Hz, 1H, H2), 6.31 (d,  $J = 1.9$  Hz, 1H, H4), 5.89 (ddt,  $J = 17.6, 9.5, 6.7$  Hz, 1H, H8), 5.06 – 4.99 (m, 2H, H9), 4.98 (s, 2H, H19), 3.82 (s, 6H, H25, H24), 3.78 (s, 3H, H26), 3.25 (dt,  $J = 6.7, 1.5$  Hz, 2H, H7), 2.56 (dd,  $J = 8.6, 6.7$  Hz, 2H, H16), 1.65 (sext,  $J = 7.5$  Hz, 2H, H17), 0.96 (t,  $J = 7.3$  Hz, 3H, H18);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.4, 154.0, 150.9, 150.4, 144.1, 138.7, 137.3, 137.1, 135.7, 130.4, 130.2, 120.7, 119.2, 116.0, 113.5, 113.1, 111.8, 107.6, 74.8, 56.3, 56.1, 55.4, 40.2, 38.0, 24.8, 14.0; HRMS (ESI+) calc. for  $\text{C}_{28}\text{H}_{33}\text{O}_5$   $[\text{M}+\text{H}]^+$  449.2323, found 449.2322.

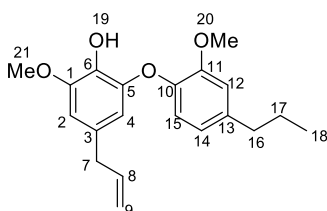
### 5-Allyl-1-methoxy-3-(2-methoxy-4-propylphenoxy)-2-(methoxymethoxy)benzene, **35**



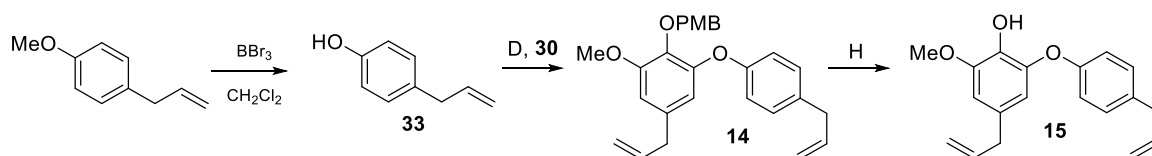
**35** was prepared according to general method D, using 5-allyl-1-iodo-3-methoxy-2-(methoxymethoxy)benzene (**4**, 167 mg, 0.5 mmol, 1.00 eq), 2-methoxy-4-propylphenol (**32**, 167 mg, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.50 eq), TMHD (52  $\mu\text{L}$ , 0.25 mmol, 0.50 eq),

cesium carbonate (326 mg, 1.0 mmol, 2.00 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified *via* flash column chromatography (petrol : EtOAc (1 : 0 → 4 : 1)), to afford **35** (47 mg, 0.126 mmol, 25%) as a pale yellow oil;  $R_f$  0.25 (petrol / EtOAc (9 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2959, 2872, 1679, 1639, 1588, 1463, 1426, 1378, 1333, 1231, 1155, 1080, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.83 – 6.77 (m, 2H, H12, H15), 6.68 (dd,  $J$  = 8.1, 1.8 Hz, 1H, H13), 6.50 – 6.45 (m, 1H, H2), 6.25 (d,  $J$  = 1.8 Hz, 1H, H4), 5.87 (ddt,  $J$  = 16.9, 10.4, 6.7 Hz, 1H, H8), 5.17 (d,  $J$  = 1.2 Hz, 2H, H23), 5.06 – 4.98 (m, 2H, H9), 3.86 (s, 3H, H21), 3.82 (s, 3H, H25), 3.57 (s, 3H, H27), 3.23 (d,  $J$  = 6.6 Hz, 2H, H7), 2.56 (t,  $J$  = 7.7 Hz, 2H, H17), 1.65 (sext,  $J$  = 7.4 Hz, 2H, H18), 0.95 (t,  $J$  = 7.3 Hz, 3H, H19);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  153.7, 151.0, 150.6, 143.5, 139.0, 137.2, 136.2, 134.4, 120.8, 119.6, 116.0, 113.0, 111.1, 107.2, 98.5, 57.2, 56.1, 56.0, 40.3, 38.0, 24.8, 14.0; HRMS (APCI) calc. for  $\text{C}_{22}\text{H}_{38}\text{O}_5\text{Na}$   $[\text{M}+\text{Na}]^+$  395.1837, found 395.1829.

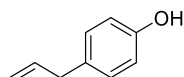
#### 4-Allyl-2-methoxy-6-(2-methoxy-4-propylphenoxy)phenol, **13**



**13** was prepared according to general method C, using 5-allyl-1-methoxy-3-(2-methoxy-4-propylphenoxy)-2-(methoxymethoxy)benzene (**35**, 47 mg, 0.13 mmol, 1.0 eq), 2 M aqueous HCl (0.4 mL) and methanol (4 mL). The reaction was complete after 24 hours. The crude residue was purified by flash column chromatography (petrol / ethyl acetate (1 : 0 → 7 : 3)) to afford **13** (22 mg, 0.07 mmol, 55%) as a colourless oil;  $R_f$  0.30 (petrol / ethyl acetate (7 : 3)); IR (thin film,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3448, 2958, 2870, 1638, 1508, 1453, 1311, 1254, 1128, 1033;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.88 (d,  $J$  = 8.1 Hz, 1H, H15), 6.79 (d,  $J$  = 1.9 Hz, 1H, H12), 6.69 (dd,  $J$  = 8.1, 1.9 Hz, 1H, H14), 6.49 (s, 1H, H2), 6.41 (s, 1H, H4), 5.97 – 5.82 (m, 2H, H8, H19), 5.08 – 4.99 (m, 2H, H9), 3.89 (s, 3H, H20), 3.87 (s, 3H, H21), 3.24 (d,  $J$  = 6.6 Hz, 2H, H7), 2.56 (t,  $J$  = 7.7 Hz, 2H, H16), 1.64 (sext,  $J$  = 7.4 Hz, 2H, H17), 0.95 (t,  $J$  = 7.3 Hz, 3H, H18);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  150.3, 147.9, 144.7, 143.9, 139.4, 137.6, 135.3, 131.1, 120.8, 119.6, 115.8, 112.9, 112.0, 107.3, 56.3, 56.1, 40.0, 38.0, 24.8, 14.0; HRMS (ESI+) calc. for  $\text{C}_{20}\text{H}_{25}\text{O}_4$   $[\text{M}+\text{H}]^+$  329.1747, found 329.1748.



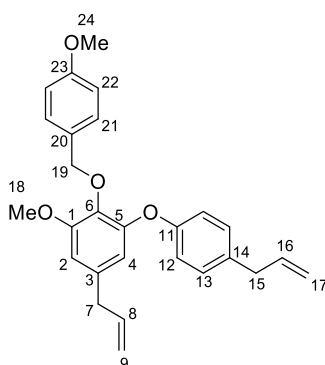
#### 4-Allylphenol, **33**



To a solution of 4-allylanisole (1.54 mL, 10.0 mmol, 1.0 eq) in dichloromethane (50 mL) at 0 °C was added boron tribromide (1.0 M in dichloromethane, 11.0 mL, 11.0 mmol, 1.1 eq) dropwise. The reaction was stirred for two hours at 0 °C before being quenched with water. The product was extracted with dichloromethane (3 × 50 mL), before being dried over  $\text{MgSO}_4$  and the solvent removed

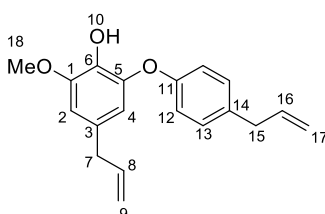
*in vacuo*. The crude residue was dissolved in diethyl ether (20 mL) and washed with 1 M aqueous NaOH (3 × 20 mL). The combined aqueous phase was then acidified to pH 5 with 5 M aqueous HCl. The product was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were dried over MgSO<sub>4</sub>, filtered, and the solvent removed *in vacuo* to afford **33** (887 mg, 6.6 mmol, 66%) as a colourless oil; R<sub>f</sub> 0.61 (pentane / ethyl acetate (4 : 1)); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.01 – 6.93 (m, 2H), 6.73 – 6.65 (m, 2H), 5.94 – 5.79 (m, 1H), 5.03 – 4.91 (m, 2H), 3.23 (d, *J* = 6.7 Hz, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 153.8, 137.9, 132.3, 128.9, 115.5, 115.3, 39.4; HRMS (ESI+) calc. for C<sub>9</sub>H<sub>9</sub>O [M-H]<sup>-</sup> 133.0659, found 133.0657. The experimental data is in good agreement with that described in the literature.<sup>10</sup>

#### 5-Allyl-1-(4-allylphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **14**



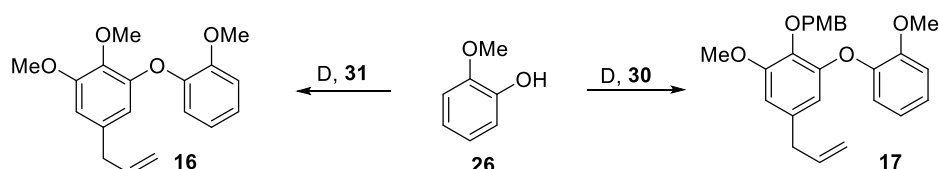
**14** was prepared according to general method D, using 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene (**30**, 205 mg, 0.5 mmol, 1.0 eq), 4-allylphenol (**33**, 134 mg, 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), TMHD (52 μL, 0.25 mmol, 0.5 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified by flash column chromatography (pentane / diethyl ether (1 : 0 → 9 : 1)) to afford **14** (58 mg, 0.14 mmol, 28%) as a colourless oil; R<sub>f</sub> 0.62 (pentane / ethyl acetate (4 : 1)); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub> 7.17 – 7.12 (m, 2H), 7.06 – 6.98 (m, 2H), 6.82 – 6.75 (m, 2H), 6.74 – 6.68 (m, 2H), 6.46 (dd, *J* = 4.3, 2.0 Hz, 1H), 6.35 (d, *J* = 2.1 Hz, 1H), 5.95 – 5.76 (m, 2H), 5.04 – 4.93 (m, 4H), 4.84 (s, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 3.28 (dd, *J* = 6.7, 1.6 Hz, 2H), 3.20 (dt, *J* = 6.7, 1.5 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ<sub>C</sub> 159.3, 156.2, 154.1, 149.8, 137.7, 137.0, 136.0, 134.0, 130.1, 129.9, 129.6, 129.5, 117.4, 116.1, 115.6, 113.5, 113.3, 108.2, 73.7, 56.1, 55.2, 40.1, 39.5; HRMS (ESI+) calc. for C<sub>27</sub>H<sub>28</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup> 439.1880, found 439.1879.

#### 4-Allyl-2-(4-allylphenoxy)-6-methoxyphenol, **15**

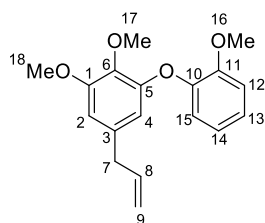


**15** was prepared according to general method H, using 5-allyl-1-(4-allylphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)benzene (**14**, 57 mg, 0.14 mmol, 1.0 eq), 1 M aqueous HCl (1.2 mL) and ethanol (2.5 mL). The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0 → 4 : 1)) to afford **15** (14 mg, 0.05 mmol, 34%) as a pale yellow oil; R<sub>f</sub> 0.44 (pentane / ethyl acetate

(4 : 1)); IR (thin film,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3325, 2361, 1601, 1505, 1453, 1433, 1314, 1222, 1147, 1083;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.08 – 7.00 (m, 2H, H12), 6.90 – 6.80 (m, 2H, H13), 6.46 (d,  $J = 1.9$  Hz, 1H, H2), 6.36 (d,  $J = 1.8$  Hz, 1H, H4), 5.96 – 5.75 (m, 2H, H8, H16), 5.34 (s, 1H, H10), 5.05 – 4.92 (m, 4H, H9, H17), 3.83 (s, 3H, H18), 3.28 (dt,  $J = 6.7, 1.5$  Hz, 2H, H15), 3.18 (dt,  $J = 6.6, 1.6$  Hz, 2H, H7);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  155.8, 147.9, 143.1, 137.6, 137.3, 135.6, 134.5, 131.5, 129.7, 117.4, 115.9, 115.7, 113.0, 107.3, 56.3, 39.9, 39.5; HRMS (ESI+) calc. for  $\text{C}_{19}\text{H}_{21}\text{O}_3$   $[\text{M}+\text{H}]^+$  297.1485, found 297.1486. The experimental data is in good agreement with that described in the literature.<sup>13</sup>

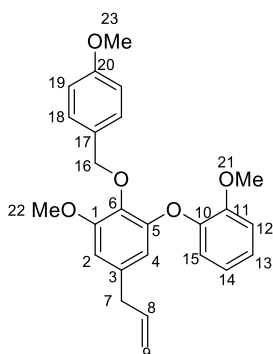


### 5-Allyl-1,2-dimethoxy-3-(2-methoxyphenoxy)benzene, **16**

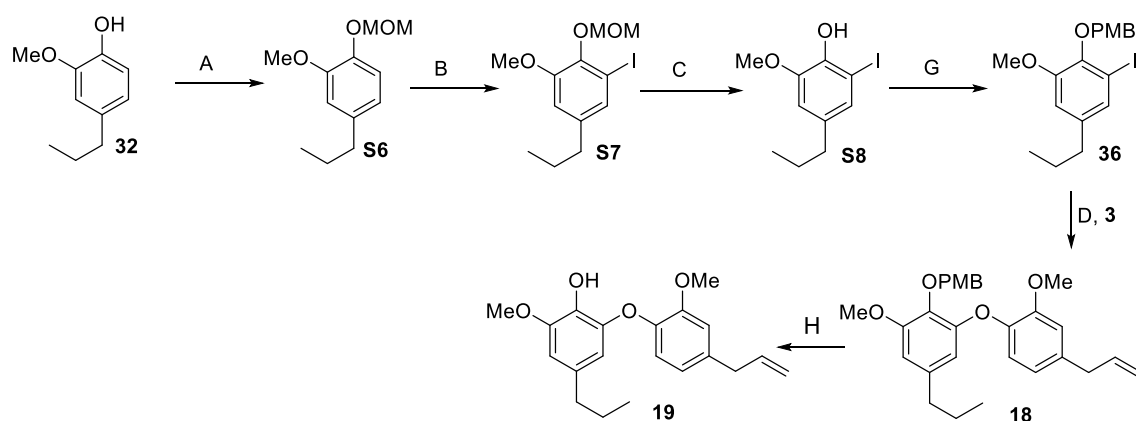


**16** was prepared according to general method D, using 5-allyl-1-iodo-2,3-dimethoxybenzene (**31**, 152 mg, 0.50 mmol, 1.0 eq), guaiacol (**26**, 110  $\mu\text{L}$ , 1.0 mmol, 2.0 eq), copper(I) chloride (25 mg, 0.25 mmol, 0.5 eq), TMHD (52  $\mu\text{L}$ , 0.25 mmol, 0.5 eq), cesium carbonate (326 mg, 1.0 mmol, 2.0 eq), NMP (0.3 mL) and dioxane (0.6 mL). The reaction was complete after two days. The crude residue was purified by flash column chromatography (petrol / ethyl acetate (1 : 0  $\rightarrow$  4 : 1)) to afford **16** (77 mg, 0.28 mmol, 52%) as a colourless oil;  $R_f$  0.24 (petrol / ethyl acetate (9 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2938, 2835, 1580, 1454, 1424, 1255, 1207, 1176, 1115, 1026;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.04 – 6.95 (m,  $J = 4.4$  Hz, 1H, H13), 6.90 (d,  $J = 8.1$  Hz, 1H, H12), 6.82 – 6.78 (m, 2H, H14, H15), 6.43 (d,  $J = 1.8$  Hz, 1H, H2), 6.23 (d,  $J = 1.8$  Hz, 1H, H4), 5.81 (m, 1H, H8), 5.01 – 4.91 (m, 2H, H9), 3.80 (s, 3H, H17), 3.79 (s, 3H, H16), 3.78 (s, 3H, H18), 3.17 (d,  $J = 6.7$  Hz, 2H, H7);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  153.6, 150.7, 150.3, 146.0, 138.2, 137.1, 135.6, 123.9, 120.9, 119.3, 116.0, 112.7, 111.7, 107.5, 61.0, 56.1, 56.0, 40.1; HRMS (APCI) calc. for  $\text{C}_{18}\text{H}_{21}\text{O}_4$   $[\text{M}+\text{H}]^+$  301.1434, found 301.1433.

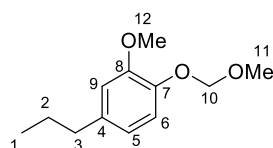
### 5-Allyl-1-methoxy-2-((4-methoxybenzyl)oxy)-3-(2-methoxyphenoxy)benzene, **17**



**17** was prepared according to general method D using 5-allyl-1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene (**30**, 410 mg, 1.0 mmol, 1.0 eq), guaiacol (**26**, 110  $\mu$ L, 2.0 mmol, 2.0 eq), copper(I) chloride (50 mg, 0.5 mmol, 0.5 eq), TMHD (104  $\mu$ L, 0.5 mmol, 0.5 eq), cesium carbonate (652 mg, 2.0 mmol, 2.0 eq), NMP (0.6 mL) and dioxane (1.2 mL). The reaction was complete after 2 days. The crude residue was purified by flash column chromatography (petrol / ethyl acetate (1 : 0  $\rightarrow$  4 : 1)) to afford **17** (180 mg, 0.44 mmol, 44%) as a colourless oil;  $R_f$  0.18 (pentane / diethyl ether (9 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2936, 2836, 1581, 1500, 1456, 1373, 1303, 1253, 1145, 1091;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.32 – 7.27 (m, 2H, H18), 7.10 – 7.01 (m, 1H, H13), 6.97 (d,  $J$  = 8.0 Hz, 1H, H12), 6.86 (td,  $J$  = 7.6, 1.4 Hz, 1H, H14), 6.83 – 6.78 (m, 3H, H15, H19), 6.50 (d,  $J$  = 1.8 Hz, 1H, H2), 6.35 (d,  $J$  = 1.8 Hz, 1H, H4), 5.97 – 5.82 (m, 1H, H8), 5.06 – 5.00 (m, 2H, H9), 4.98 (s, 2H, H16), 3.84 (s, 3H, H23), 3.83 (s, 3H, H21), 3.78 (s, 3H, H22), 3.26 (d,  $J$  = 6.6 Hz, 2H, H7);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.2, 154.0, 150.4, 150.3, 146.3, 137.1, 135.3, 130.2, 130.2, 130.1, 123.6, 120.9, 118.9, 116.0, 113.4, 112.6, 112.1, 107.8, 74.7, 56.1, 56.0, 55.2, 40.1; HRMS (ESI+) calc. for  $\text{C}_{25}\text{H}_{27}\text{O}_5$   $[\text{M}+\text{H}]^+$  407.1853, found 407.1855.

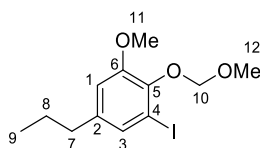


## 2-Methoxy-1-(methoxymethoxy)-4-propylbenzene, **S6**



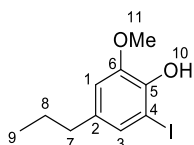
**S6** was prepared according to general method A, using 2-methoxy-4-propylphenol (**32**, 200 mg, 1.2 mmol, 1.0 eq), chloromethyl methyl ether (119  $\mu$ L, 1.6 mmol, 1.3 eq), diisopropylethylamine (335  $\mu$ L, 1.9 mmol, 1.6 eq) and dichloromethane (1.4 mL). The reaction was complete after 20 hours, to afford on work up **S6** (225 mg, 1.1 mmol, 89%) as a yellow oil;  $R_f$  0.54 (pentane / ethyl acetate (9 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2957, 2872, 1512, 1464, 1418, 1378, 1262, 1226, 1134, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.05 (d,  $J$  = 8.1 Hz, 1H, H6), 6.72 (s, 1H, H9), 6.70 (d,  $J$  = 8.1 Hz, 1H, H5), 5.19 (s, 2H, H10), 3.87 (s, 3H, H11), 3.51 (s, 3H, H12), 2.53 (t,  $J$  = 7.7 Hz, 2H, H3), 1.63 (h,  $J$  = 7.5 Hz, 2H, H2), 0.94 (t,  $J$  = 7.3 Hz, 3H, H1);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  149.7, 144.5, 137.4, 120.6, 116.7, 112.3, 95.8, 56.2, 55.9, 37.9, 24.8, 14.0; HRMS (Ammonia Cl) calc. for  $\text{C}_{12}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$  211.1329, found 211.1327.

### 1-iodo-3-methoxy-2-(methoxymethoxy)-5-propylbenzene, **S7**



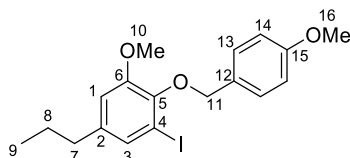
**S7** was prepared according to general method B, using 2-methoxy-1-(methoxymethoxy)-4-propylbenzene (**S6**, 150 mg, 0.7 mmol, 1.0 eq), *s*-BuLi (1.3 M in hexanes, 0.82 mL, 1.1 mmol, 1.5 eq), TMEDA (160  $\mu$ L, 1.1 mmol, 1.5 eq), iodine (272 mg, 1.1 mmol, 1.5 eq) and THF (1.0 + 0.3 mL). The crude residue was purified by flash column chromatography (petrol / ethyl acetate (1 : 0  $\rightarrow$  9 : 1)) to afford **S7** (192 mg, 0.6 mmol, 60%) as a pale yellow oil;  $R_f$  0.65 (pentane / ethyl acetate (4 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2958, 2870, 1591, 1560, 1462, 1340, 1265, 1200, 1158, 1142;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.19 (d,  $J$  = 1.9 Hz, 1H, H1), 6.68 (d,  $J$  = 2.0 Hz, 1H, H3), 5.12 (s, 2H, H10), 3.82 (s, 3H, H11), 3.67 (s, 3H, H12), 2.48 (dd,  $J$  = 8.6, 6.7 Hz, 2H, H7), 1.67 – 1.55 (m, 2H, H8), 0.93 (t,  $J$  = 7.3 Hz, 4H, H9);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  152.1, 143.9, 141.0, 130.7, 113.7, 98.8, 92.5, 58.5, 56.0, 37.5, 24.6, 13.9; HRMS (ESI+) calc. for  $\text{C}_{12}\text{H}_{17}\text{O}_3\text{I}\text{Na}$   $[\text{M}+\text{Na}]^+$  358.0115, found 359.0116.

### 2-iodo-6-methoxy-4-propylphenol, **S8**



**S8** was prepared according to general method C, using 1-iodo-3-methoxy-2-(methoxymethoxy)-5-propylbenzene (**S7**, 192 mg, 0.6 mmol, 1.0 eq), 2M aqueous HCl (1.7 mL) and methanol (8.4 mL). The reaction was complete after 20 hours. The crude residue was purified by flash column chromatography (pentane / diethyl ether (9 : 1  $\rightarrow$  4 : 1)) to afford **S8** (129 mg, 0.4 mmol, 77%) as a colourless wax;  $R_f$  0.31 (pentane / diethyl ether (4 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3481, 2997, 1602, 1493, 1462, 1360, 1272, 1173, 1095, 1044;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.04 (s, 1H, H1), 6.56 (s, 1H, H3), 5.84 (s, 1H, H10), 3.79 (s, 3H, H11), 2.40 (t,  $J$  = 7.7 Hz, 2H, H7), 1.52 (sext,  $J$  = 7.3 Hz, 2H, H8), 0.85 (t,  $J$  = 7.3 Hz, 3H, H9);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  145.8, 143.6, 136.4, 130.0, 111.2, 81.1, 56.2, 37.3, 24.7, 13.7; HRMS (ESI-) calc. for  $\text{C}_{10}\text{H}_{12}\text{O}_2\text{I}$   $[\text{M}-\text{H}]^-$  290.9888, found 290.9887.

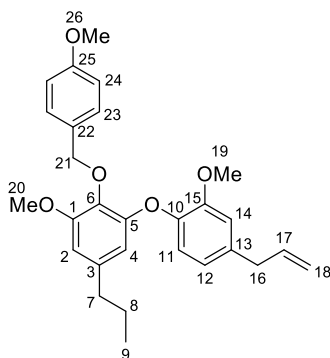
### 1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene, **36**



**36** was prepared according to general method G, using 2-iodo-6-methoxy-4-propylphenol (**S8**, 128 mg, 0.44 mmol, 1.0 eq), *para*-methoxybenzyl chloride (71  $\mu$ L, 0.53 mmol, 1.2 eq), potassium carbonate (151 mg, 1.10 mmol, 2.5 eq) and DMF (3.3 mL). The reaction was complete after 4 hours. The crude residue was purified by flash column chromatography (pentane / diethyl ether (1 : 0  $\rightarrow$  9 : 1)) to afford **36** (126 mg, 0.31 mmol, 70%), as a colourless wax;  $R_f$  0.40 (pentane / ethyl acetate (9 : 1)); IR (neat,

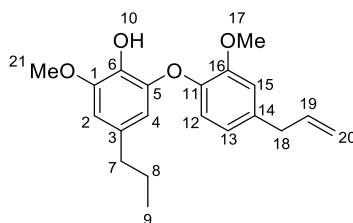
$\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3003, 2831, 1611, 1559, 1512, 1460, 1303, 1248, 1171, 1034;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.55 – 7.47 (m, 2H, H13), 7.19 (d,  $J$  = 1.8 Hz, 1H, H1), 6.96 – 6.88 (m, 2H, H14), 6.71 (d,  $J$  = 1.9 Hz, 1H, H3), 4.92 (s, 2H, H11), 3.85 (s, 3H, H16), 3.82 (s, 3H, H10), 2.50 (dd,  $J$  = 8.6, 6.7 Hz, 2H, H7), 1.63 (sext,  $J$  = 7.6 Hz, 2H, H8), 0.95 (t,  $J$  = 7.3 Hz, 3H, H9);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.6, 152.6, 145.9, 140.9, 130.4, 130.4, 129.2, 113.8, 113.4, 93.0, 73.9, 56.1, 55.4, 37.5, 23.9, 13.9; HRMS (ESI+) calc. for  $\text{C}_{18}\text{H}_{21}\text{O}_3\text{Na}$   $[\text{M}+\text{Na}]^+$  435.0428, found 435.0427.

### 1-(4-Allyl-2-methoxyphenoxy)-3-Methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene, **18**



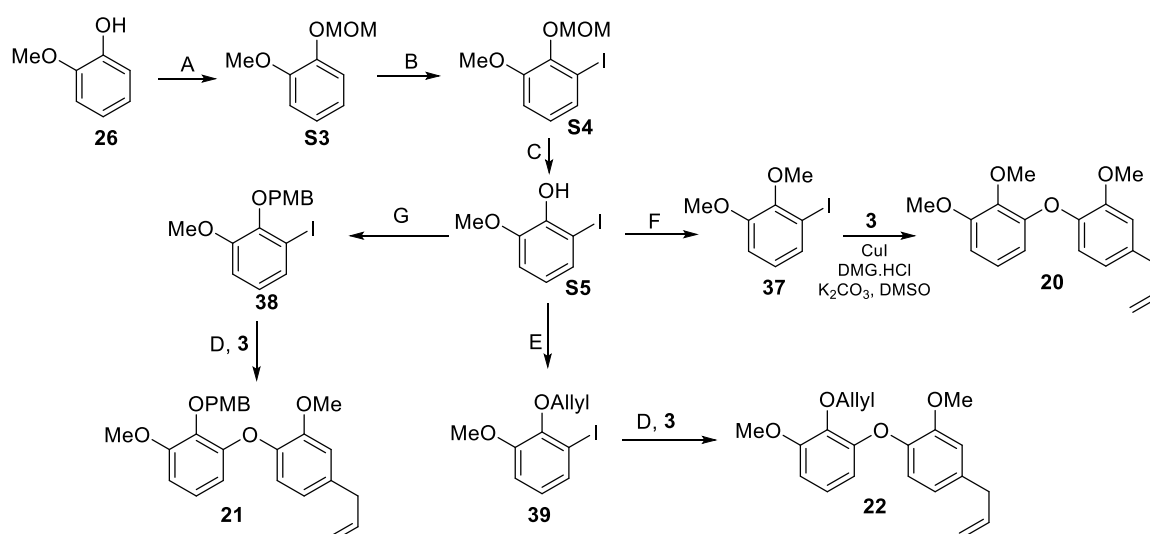
**18** was prepared according to general method D, using 1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene (**36**, 95 mg, 0.23 mmol, 1.0 eq), eugenol (**3**, 71  $\mu\text{L}$ , 0.46 mmol, 2.0 eq), copper(I) chloride (11 mg, 0.12 mmol, 0.5 eq), TMHD (24  $\mu\text{L}$ , 0.12 mmol, 0.5 eq), cesium carbonate (151 mg, 0.46 mmol, 2.0 eq), NMP (0.14 mL) and dioxane (0.28 mL). The reaction was complete after three days. The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0  $\rightarrow$  4 : 1)) to afford **18** (56 mg, 0.12 mmol, 54%) as a white solid; MP 52-55  $^{\circ}\text{C}$ ;  $R_f$  0.23 (pentane / ethyl acetate (9 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3001, 2870, 1609, 1506, 1463, 1421, 1375, 1248, 1152, 1080;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.35 – 7.27 (m, 2H, H23), 6.84 – 6.77 (m, 3H, H14, H24), 6.74 (d,  $J$  = 8.1 Hz, 1H, H11), 6.67 (dd,  $J$  = 8.1, 1.9 Hz, 1H, H12), 6.47 (d,  $J$  = 1.9 Hz, 1H, H2), 6.31 (d,  $J$  = 1.9 Hz, 1H, H4), 5.98 (ddt,  $J$  = 16.8, 10.1, 6.7 Hz, 1H, H17), 5.15 – 5.04 (m, 2H, H18), 4.97 (s, 2H, H21), 3.82 (s, 3H, H26), 3.82 (s, 3H, H19), 3.78 (s, 3H, H20), 3.37 (dt,  $J$  = 6.8, 1.5 Hz, 2H, H16), 2.44 (dd,  $J$  = 8.6, 6.7 Hz, 2H, H7), 1.56 (dq,  $J$  = 13.7, 7.4 Hz, 2H, H8), 0.89 (t,  $J$  = 7.3 Hz, 3H, H9);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.3, 153.9, 150.5, 150.4, 144.7, 138.5, 137.7, 136.8, 135.7, 130.4, 130.2, 120.8, 119.0, 116.0, 113.5, 113.0, 111.8, 107.7, 74.8, 56.2, 56.1, 55.4, 40.1, 38.2, 24.6, 13.9; HRMS (ESI+) calc. for  $\text{C}_{28}\text{H}_{33}\text{O}_5$   $[\text{M}+\text{H}]^+$  449.2323, found 449.2329.

### 2-(4-Allyl-2-methoxyphenoxy)-6-Methoxy-4-propylphenol, **19**

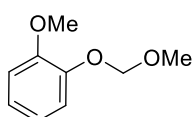


**19** was prepared according to general method H, using 1-(4-allyl-2-methoxyphenoxy)-3-methoxy-2-((4-methoxybenzyl)oxy)-5-propylbenzene (**18**, 30 mg, 0.07 mmol, 1.0 eq), 1 M aqueous HCl (0.5 mL) and ethanol (1.4 mL). The crude residue was purified by flash column chromatography (pentane /

ethyl acetate (1 : 0 → 4 : 1)) to afford **19** (17 mg, 0.05 mmol, 75%) as a colourless oil;  $R_f$  0.32 (pentane / ethyl acetate (4 : 1)); IR (thin film,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3441, 2931, 1596, 1507, 1452, 1431, 1309, 1238, 1151, 1092;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.88 (d,  $J$  = 8.1 Hz, 1H, H12), 6.80 (d,  $J$  = 2.0 Hz, 1H, H15), 6.70 (dd,  $J$  = 8.1, 1.9 Hz, 1H, H13), 6.49 (d,  $J$  = 1.8 Hz, 1H, H2), 6.39 (d,  $J$  = 1.9 Hz, 1H, H4), 5.97 (ddt,  $J$  = 16.9, 10.1, 6.7 Hz, 1H, H19), 5.79 (s, 1H, H10), 5.15 – 5.04 (m, 2H, H20), 3.89 (s, 3H, H21), 3.87 (s, 3H, H17), 3.37 (dt,  $J$  = 6.7, 1.6 Hz, 2H, H18), 2.44 (dd,  $J$  = 8.6, 6.7 Hz, 2H, H7), 1.55 (dq,  $J$  = 16.0, 7.6 Hz, 2H, H8), 0.89 (t,  $J$  = 7.3 Hz, 3H, H9);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  150.5, 147.4, 144.4, 144.3, 137.4, 136.4, 134.9, 134.0, 120.9, 119.5, 116.1, 112.9, 111.8, 107.3, 56.3, 56.1, 40.1, 38.0, 24.8, 13.8; HRMS (ESI+) calc. for  $\text{C}_{20}\text{H}_{25}\text{O}_4$   $[\text{M}+\text{H}]^+$  329.1747, found 329.1747.

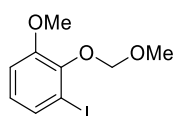


### 1-Methoxy-2-(methoxymethoxy)benzene, **S3**



**S3** was prepared according to general method A, using guaiacol (3.3 mL, 29.7 mmol, 1.0 eq), DIPEA (8.3 mL, 47.6 mmol, 1.6 eq), chloromethyl methyl ether (2.9 mL, 38.7 mmol, 1.3 eq), and  $\text{CH}_2\text{Cl}_2$  (35 mL) the reaction was complete after 18 hours to afford **S3** (2.99 g, 29.7 mmol, 99%) as a yellow oil, which was used without further purification;  $R_f$  0.36 (petrol / EtOAc (9 : 1));  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.19–7.12 (m, 1H), 7.03–6.94 (m, 1H), 6.93–6.81 (m, 2H), 5.22 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  149.7, 146.5, 122.5, 120.9, 116.5, 111.8, 95.5, 56.1, 55.8. Experimental data is in good agreement with that described in the literature.<sup>6</sup>

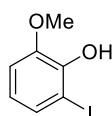
### 1-Iodo-3-methoxy-2-(methoxymethoxy)benzene, **S4**



**S4** was prepared according to general method B, using 1-methoxy-2-(methoxymethoxy)benzene (**S3**,

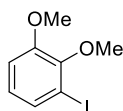
2.10 g, 10 mmol, 1.0 eq), *s*-BuLi (1.3 M in hexanes, 12 mL, 15 mmol, 1.5 eq), TMEDA (2.3 mL, 15 mmol, 1.5 eq), iodine (3.8 g, 15 mmol, 1.5 eq) and THF (15 + 5 mL). The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0 → 4 : 1)) to afford **S4** (2.1 g, 7.1 mmol, 71%) as a colourless oil;  $R_f$  0.54 (pentane / ethyl acetate (9 : 1));  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.37 (dd,  $J = 7.9, 1.4$  Hz, 1H), 6.88 (dd,  $J = 8.2, 1.4$  Hz, 1H), 6.79 (td,  $J = 8.2, 1.4$  Hz, 1H), 5.17 (s, 2H), 3.83 (s, 3H), 3.68 (s, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  152.6, 146.0, 131.1, 126.0, 112.9, 98.8, 92.8, 58.5, 56.1; HRMS (APCI) calc. for  $\text{C}_9\text{H}_{10}\text{O}_3\text{I}$   $[\text{M}-\text{H}]^-$  292.9680, found 292.9673. The experimental data is in good agreement with that described in the literature.<sup>7</sup>

### 2-Iodo-6-methoxyphenol, S5



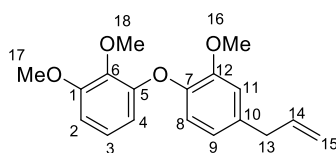
**S5** was prepared according to general method C, using 1-iodo-3-methoxy-2-(methoxymethoxy)benzene (**S4**, 3.00 g, 10.2 mmol, 1.0 eq), 2 M aqueous HCl (30 mL) and methanol (150 mL). The reaction was complete after 15 hours to afford on work up **S5** (2.50 g, 10.1 mmol, 98%) as a white solid; MP 46-49 °C;  $R_f$  0.41 (pentane / ethyl acetate (4 : 1));  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.28 (dd,  $J = 8.1, 1.4$  Hz, 1H), 6.81 (dd,  $J = 8.1, 1.4$  Hz, 1H), 6.62 (t,  $J = 8.1$ , 1H), 6.14 (s, 1H), 3.86 (d,  $J = 1.4$  Hz, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  146.2, 145.7, 130.6, 121.7, 110.7, 81.5, 56.3; HRMS (ESI-) calc. for  $\text{C}_7\text{H}_6\text{O}_2\text{I}$   $[\text{M}-\text{H}]^-$  248.9418, found 248.9420. The experimental data is in good agreement with that described in the literature.<sup>8</sup>

### 1-Iodo-2,3-dimethoxybenzene, 37



**37** was prepared according to general method F using 2-iodo-6-methoxyphenol (**S5**, 300 mg, 1.2 mmol, 1.0 eq), methyl iodide (105  $\mu\text{L}$ , 1.7 mmol, 1.4 eq), potassium carbonate (663 mg, 4.8 mmol, 4.0 eq) and DMF (1.75 mL). The reaction was complete after 20 hours to afford on work up **37** (296 mg, 1.1 mmol, 93%) as a colourless wax, which was used without further purification;  $R_f$  0.49 (pentane / diethyl ether (4 : 1));  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.34 (dd,  $J = 7.9, 1.5$  Hz, 1H), 6.88 (dd,  $J = 8.2, 1.5$  Hz, 1H), 6.79 (t,  $J = 8.1$  Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  153.0, 149.1, 130.6, 126.0, 112.9, 92.7, 60.5, 56.0; HRMS (EI) calc. for  $\text{C}_8\text{H}_9\text{O}_2\text{I}$   $[\text{M}]^+$  263.9642, found 263.9643. The experimental data is in good agreement with that described in the literature.<sup>9</sup>

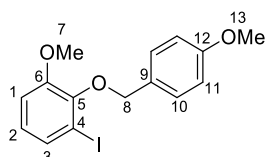
### 1-(4-allyl-2-methoxyphenoxy)-2,3-dimethoxybenzene, 20



CuI (9.5 mg, 0.050 mmol, 10 mol%), *N,N*-dimethylglycine hydrochloride (21 mg, 0.15 mmol, 30 mol%), and  $\text{K}_2\text{CO}_3$  (138 mg, 1.0 mmol, 2.0 eq) were loaded in a dry vial fitted with a septum. The vial was evacuated and purged with Ar three times. DMSO (1.0 mL) was added, followed by 1-iodo-2,3-

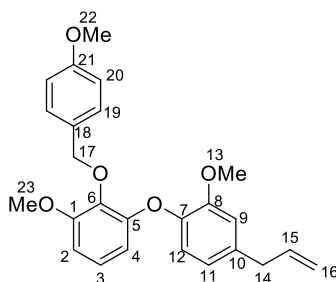
dimethoxybenzene (**37**, 132 mg, 0.50 mmol, 1.0 eq) and eugenol (**3**, 115  $\mu$ L, 0.75 mmol, 1.5 eq). Under an Ar blanket, the septum was replaced with a tightly fastened screwcap. The reaction mixture was stirred at 80 °C for two days, after which time TLC indicated consumption of the starting material. After cooling to room temperature, the mixture was diluted with diethyl ether (20 mL) and water (40 mL). The layers were separated, and the aqueous solution extracted with diethyl ether (3  $\times$  10 mL). The combined ethereal layers were washed with NaOH (1 M, 3  $\times$  10 mL) and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (petrol / diethyl ether (9 : 1  $\rightarrow$  3 : 1)) to afford **20** (67 mg, 0.223 mmol, 45%) as a colourless oil; *R*<sub>f</sub> 0.24 (diethyl ether/petrol (1:4)); IR (thin film,  $\nu_{\max}$  / cm<sup>-1</sup>) 2937, 2835, 1589, 1470, 1210, 1080, 731; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  6.89 (t, *J* = 8.3 Hz, 1H, H3), 6.84 (d, *J* = 8.1 Hz, 1H, H8), 6.81 (d, *J* = 1.9 Hz, 1H, H11), 6.71 (dd, *J* = 8.1, 2.0 Hz, 1H, H9), 6.65 (dd, *J* = 8.3, 1.3 Hz, 1H, H2), 6.41 (dd, *J* = 8.4, 1.4 Hz, 1H, H4), 5.98 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H14), 5.16 – 5.07 (m, 2H, H15), 3.91 (s, 3H, H16), 3.88 (s, 3H, H17), 3.82 (s, 3H, H18), 3.37 (d, *J* = 6.7 Hz, 2H, *z* H13); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  153.9, 151.3, 150.8, 143.9, 139.7, 137.4, 136.4, 123.4, 120.8, 120.0, 116.0, 113.2, 111.0, 106.9, 61.1, 56.2, 56.0, 40.0; HRMS (ESI+) calc. for C<sub>18</sub>H<sub>21</sub>O<sub>4</sub> [M+H]<sup>+</sup> 301.1434, found 301.1435.

### 1-Iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene, **38**



**38** was prepared according to general method G, using 2-iodo-6-methoxyphenol (**S5**, 2.00 g, 8.0 mmol, 1.0 eq), *para*-methoxybenzyl chloride (1.3 mL, 9.6 mmol, 1.2 eq), potassium carbonate (2.8 g, 20.0 mmol, 2.5 eq) and DMF (50 mL). The reaction was complete after two hours. The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0  $\rightarrow$  9 : 1)) to afford **38** (2.70 g, 7.3 mmol, 91%) as a colourless oil; *R*<sub>f</sub> 0.39 (petrol / ethyl acetate (4 : 1)); IR (neat,  $\nu_{\max}$  / cm<sup>-1</sup>) 2936, 2835, 1612, 1513, 1465, 1371, 1293, 1248, 1110, 1029; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  7.57 – 7.50 (m, 2H, H10), 7.39 (d, *J* = 7.8 Hz, 1H, H1), 6.98 – 6.89 (m, 3H, H3, H11), 6.83 (t, *J* = 8.1, 1H, H2), 4.98 (s, 2H, H8), 3.89 (s, 3H, H7), 3.85 (s, 3H, H13); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  159.6, 153.1, 147.8, 130.7, 130.4, 129.3, 126.0, 113.7, 112.8, 93.3, 74.2, 56.0, 55.3; HRMS (ESI+) calc. for C<sub>15</sub>H<sub>15</sub>O<sub>3</sub>INa [M+Na]<sup>+</sup> 392.9958, found 392.9956.

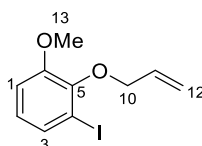
### 1-(4-Allyl-2-methoxyphenoxy)-3-Methoxy-2-((4-methoxybenzyl)oxy)benzene, **21**



**21** was prepared according to general method D, using 1-iodo-3-methoxy-2-((4-methoxybenzyl)oxy)benzene (**38**, 1.00 g, 2.7 mmol, 1.0 eq), eugenol, **3** (831  $\mu$ L, 5.4 mmol, 2.0 eq),

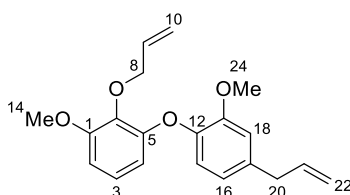
copper(I) chloride (134 mg, 1.4 mmol, 0.5 eq), cesium carbonate (1.76 g, 5.4 mmol, 2.0 eq), TMHD (249  $\mu$ L, 1.4 mmol, 0.5 eq), NMP (2.0 mL) and dioxane (4.0 mL). The reaction was complete after three days. The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0  $\rightarrow$  4 : 1)) to afford **21** (575 mg, 1.4 mmol, 52%) as a colourless oil;  $R_f$  0.15 (pentane / diethyl ether (4 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2937, 2836, 1588, 1708, 1469, 1419, 1373, 1243, 1152, 1033;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.38 – 7.28 (m, 2H, H20), 6.91 (t,  $J$  = 8.3 Hz, 1H, H3), 6.85 – 6.76 (m, 4H, H9, H12, H19), 6.70 (dd,  $J$  = 8.1, 2.0 Hz, 1H, H11), 6.65 (dd,  $J$  = 8.3, 1.4 Hz, 1H, H2), 6.45 (dd,  $J$  = 8.3, 1.6 Hz, 1H, H4), 5.99 (ddt,  $J$  = 16.8, 10.1, 6.7 Hz, 1H, H15), 5.15–5.07 (m, 2H, H16), 5.04 (s, 2H, H17), 3.84 (s, 3H, H22), 3.82 (s, 3H, H13), 3.79 (s, 3H, H23), 3.38 (dd,  $J$  = 6.6, 1.6 Hz, 2H, H14);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  159.4, 154.4, 151.5, 150.8, 149.4, 144.2, 138.7, 137.6, 136.2, 130.3, 123.5, 120.9, 119.7, 116.0, 113.5, 113.2, 111.3, 107.2, 74.7, 56.3, 56.1, 55.4, 40.8; HRMS (ESI $^-$ ) calc. for  $\text{C}_{25}\text{H}_{25}\text{O}_5$  [ $\text{M}-\text{H}$ ] $^-$  405.1708, found 405.1705.

### 2-(Allyloxy)-1-iodo-3-methoxybenzene, **39**



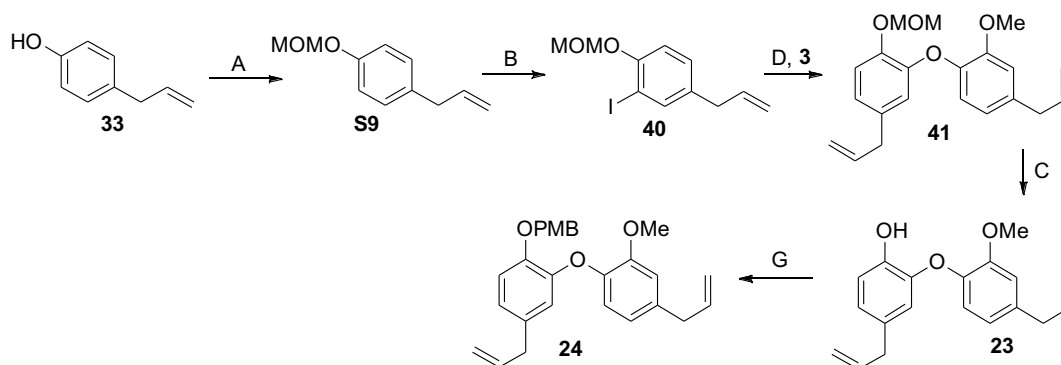
**39** was prepared according to general method E, using 2-iodo-6-methoxyphenol (**S5**, 100 mg, 0.4 mmol, 1.0 eq), potassium carbonate (138 mg, 1.0 mmol, 2.5 eq), allyl bromide (52  $\mu$ L, 0.6 mmol, 1.5 eq) and DMF (0.4 mL). The reaction was complete after three hours. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0  $\rightarrow$  19 : 1)) to afford **39** (60 mg, 0.2 mmol, 52%) as a colourless oil;  $R_f$  0.44 (petrol / EtOAc (9 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2937, 1578, 1467, 1445, 1433, 1419, 1355, 1292, 1259, 1221, 1176, 1142, 1078, 1029;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.35 (dt,  $J$  = 7.9, 1.1 Hz, 1H, H1), 6.88 (dd,  $J$  = 8.2, 1.1 Hz, 1H, H3), 6.79 (t,  $J$  = 8.2 Hz, 1H, H2), 6.25–6.10 (m, 1H, H11), 5.41 (dq,  $J$  = 17.1, 1.3 Hz, 1H, H12), 5.31–5.20 (m, 1H, H12), 4.52 (dt,  $J$  = 5.7, 1.3 Hz, 2H, H10), 3.84 (s, 3H, H13);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  153.0, 147.9, 134.0, 130.7, 126.0, 118.2, 112.8, 93.3, 74.0, 56.1; HRMS (Methane Cl) calc. for  $\text{C}_{10}\text{H}_{12}\text{IO}_2$  [ $\text{M}+\text{H}$ ] $^+$  290.9876, found 290.9864.

### 1-(4-Allyl-2-methoxyphenoxy)-2-(allyloxy)-3-methoxybenzene, **22**

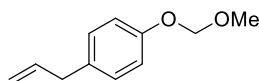


**22** was prepared according to general method D, using 2-(allyloxy)-1-iodo-3-methoxybenzene (**39**, 1.00 g, 3.45 mmol, 1.0 eq), eugenol (**3**, 1.06 mL, 6.89 mmol, 2.0 eq), copper(I) chloride (171 mg, 1.72 mmol, 0.5 eq), TMHD (360  $\mu$ L, 1.72 mmol, 0.5 eq), cesium carbonate (2.25 g, 6.89 mmol, 2.0 eq), NMP (2.0 mL), and dioxane (4.0 mL). The reaction was complete after 3 days. The crude residue was purified *via* flash column chromatography (petrol / EtOAc (1 : 0  $\rightarrow$  9 : 1), to afford **22** (635 mg, 1.95 mmol, 52%) as a colourless oil;  $R_f$  0.29 (petrol / EtOAc (9 : 1)); IR (thin film,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2936, 2361, 1594, 1507, 1491, 1471, 1439, 1419, 1265, 1244, 1211, 1153, 1128, 1083, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.90 (t,  $J$  = 8.3 Hz, 1H, H3), 6.82 (d,  $J$  = 8.1 Hz, 1H, H15), 6.80 (d,  $J$  = 1.9 Hz, 1H, H18), 6.70 (dd,  $J$  = 8.1, 1.9 Hz, 1H, H16), 6.65 (dd,  $J$  = 8.3, 1.4 Hz, 1H, H4), 6.42 (dd,  $J$  = 8.3, 1.4 Hz, 1H, H2), 6.07 (ddt,  $J$  = 17.2,

10.4, 6.0 Hz, 1H, H9), 5.97 (ddt,  $J = 16.8, 10.1, 6.7$  Hz, 1H, H21), 5.26 (dq,  $J = 17.2, 1.6$  Hz, 1H, H10), 5.16–5.05 (m, 3H, H10, H22), 4.60 (dt,  $J = 6.1, 1.3$  Hz, 2H, H8), 3.87 (s, 3H, H14), 3.82 (s, 3H, H24), 3.37 (dt,  $J = 6.7, 1.4$  Hz, 2H, H20);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  154.2, 151.5, 150.8, 144.1, 138.5, 137.5, 136.3, 134.7, 123.5, 120.9, 119.9, 117.6, 116.0, 113.2, 111.2, 107.0, 74.4, 56.3, 56.1, 40.1; HRMS (ES+) calc. for  $\text{C}_{20}\text{H}_{23}\text{O}_4$   $[\text{M}+\text{H}]^+$  327.1591, found 327.1589.

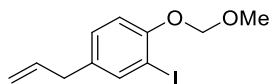


#### 1-Allyl-4-(methoxymethoxy)benzene, **S9**



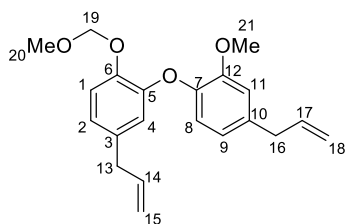
**S9** was prepared according to general method A, using 4-allylphenol (**33**, 134 mg, 1.0 mmol, 1.0 eq), chloromethyl methyl ether (99  $\mu\text{L}$ , 1.3 mmol, 1.3 eq), DIPEA (279  $\mu\text{L}$ , 1.6 mmol, 1.6 eq) and dichloromethane (1.2 mL). The reaction was complete after 24 hours. The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0  $\rightarrow$  98 : 2)) to afford **S9** (49 mg, 0.27 mmol, 27%) as a colourless oil;  $R_f$  0.26 (pentane / diethyl ether (98 : 2));  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.12 (d,  $J = 8.2$  Hz, 2H), 6.99 (d,  $J = 8.3$  Hz, 2H), 5.96 (ddtd,  $J = 16.9, 10.0, 6.6, 1.1$  Hz, 1H), 5.16 (s, 2H), 5.12 – 5.02 (m, 2H), 3.49 (s, 3H), 3.35 (d,  $J = 6.6$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  155.8, 137.9, 133.6, 129.7, 116.4, 115.7, 94.7, 56.0, 39.5; HRMS (APCI) calc. for  $\text{C}_{12}\text{H}_{15}\text{O}_2$   $[\text{M}+\text{H}]^+$  191.1067, found 191.1069. The experimental data is in good agreement with that described in the literature.<sup>11</sup>

#### 4-Allyl-2-iodo-1-(methoxymethoxy)benzene, **40**



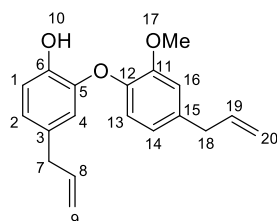
**40** was prepared according to general method B, using 1-allyl-4-(methoxymethoxy)benzene (**S9**, 535 mg, 3.0 mmol, 1.0 eq), *s*-BuLi (1.3 M in hexanes, 3.5 mL, 4.5 mmol, 1.5 eq), TMEDA (675  $\mu\text{L}$ , 4.5 mmol, 1.5 eq), iodine (1.1 g, 4.5 mmol, 1.4 eq) and THF (4 + 2 mL) to give on work-up **40** (529 mg, 1.7 mmol, 58 %) as a yellow oil;  $R_f$  0.81 (pentane / ethyl acetate (4 : 1));  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 (d,  $J = 2.1$  Hz, 1H), 7.09 (dd,  $J = 8.4, 2.2$  Hz, 1H), 6.99 (d,  $J = 8.4$  Hz, 1H), 5.97 – 5.86 (m, 1H), 5.21 (s, 2H), 5.11 – 5.02 (m, 2H), 3.51 (s, 3H), 3.30 (d,  $J = 6.7$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  154.5, 139.5, 137.1, 135.7, 129.7, 116.3, 115.0, 95.2, 87.4, 56.1, 38.9; HRMS (APCI) calc. for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{I}$   $[\text{M}+\text{H}]^+$  303.9955, found 303.9960. The experimental data is in good agreement with that described in the literature.<sup>12</sup>

#### 4-Allyl-1-(5-allyl-2-(methoxymethoxy)phenoxy)-2-methoxybenzene, **41**



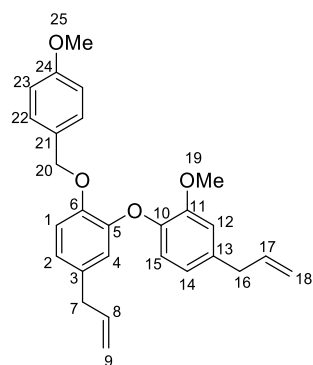
**41** was prepared according to general method D, using 4-allyl-2-iodo-1-(methoxymethoxy)benzene (**40**, 100 mg, 0.33 mmol, 1.0 eq), eugenol (**3**, 101  $\mu$ L, 0.66 mmol, 2.0 eq), copper(I) chloride (16 mg, 0.16 mmol, 0.5 eq), cesium carbonate (214 mg, 0.66 mmol, 2.0 eq), TMHD (34  $\mu$ L, 0.16 mmol, 0.5 eq), NMP (0.2 mL) and dioxane (0.4 mL). The reaction was complete after 2 days. The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0  $\rightarrow$  9 : 1)) to afford **41** (79 mg, 0.23 mmol, 71%) as a colourless oil;  $R_f$  0.48 (pentane / ethyl acetate (4 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 2901, 2828, 1592, 1505, 1421, 1256, 1212, 1153, 1128, 1076;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$  7.13 (d,  $J$  = 8.3 Hz, 1H, H1), 6.84 (dd,  $J$  = 8.3, 1.8 Hz, 1H, H2), 6.80 (d,  $J$  = 1.8 Hz, 1H, H4), 6.75 (d,  $J$  = 8.1 Hz, 1H, H8), 6.70 – 6.66 (m, 2H, H9, H11), 5.98 (ddt,  $J$  = 16.3, 9.6, 6.4 Hz, 1H, H17), 5.88 (ddt,  $J$  = 17.5, 9.5, 6.6 Hz, 1H, H14), 5.18 (s, 2H, H19), 5.14 – 4.96 (m, 4H, H15, H18), 3.84 (s, 3H, H21), 3.45 (s, 3H, H20), 3.37 (dt,  $J$  = 6.7, 1.5 Hz, 2H, H16), 3.25 (dt,  $J$  = 6.6, 1.5 Hz, 2H, H13);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta_{\text{C}}$  150.4, 147.1, 146.3, 144.4, 137.6, 137.5, 135.9, 134.8, 123.8, 120.8, 119.5, 118.8, 117.8, 116.0, 115.8, 113.0, 95.7, 56.3, 56.0, 40.1, 39.5; HRMS (ESI+) calc. for  $\text{C}_{21}\text{H}_{24}\text{O}_4\text{Na}$   $[\text{M}+\text{Na}]^+$  363.1567, found 363.1566.

#### 4-Allyl-2-(4-allyl-2-methoxyphenoxy)phenol, **23**

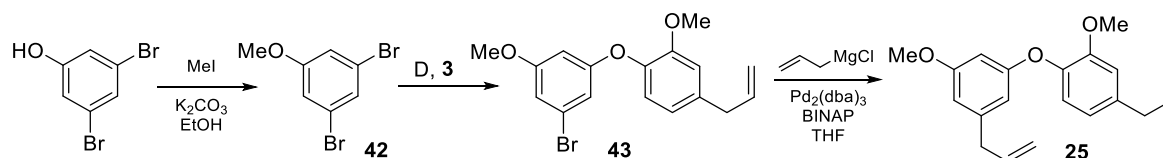


**23** was prepared according to general method C, using 4-allyl-1-(5-allyl-2-(methoxymethoxy)phenoxy)-2-methoxybenzene (**41**, 50 mg, 0.15 mmol, 1.0 eq), 1 M aqueous HCl (0.3 mL) and methanol (1.4 mL). The reaction was complete after 24 hours to afford on work-up **23** (44 mg, 0.15 mmol, >99%) as a colourless oil;  $R_f$  0.56 (pentane / ethyl acetate (4 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3437, 2917, 1596, 1506, 1434, 1360, 1264, 1215, 1186, 1126;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$  6.98 (d,  $J$  = 8.1 Hz, 1H, H1), 6.92 (d,  $J$  = 8.2 Hz, 1H, H13), 6.85 – 6.78 (m, 2H, H4, H14), 6.75 (dd,  $J$  = 8.1, 2.0 Hz, 1H, H2), 6.71 (d,  $J$  = 2.1 Hz, 1H, H16), 6.08 (s, 1H, H10), 6.04 – 5.81 (m, 2H, H8, H19), 5.15 – 5.06 (m, 2H, H20), 5.05 – 4.96 (m, 2H, H9), 3.86 (s, 3H, H17), 3.38 (dt,  $J$  = 6.7, 1.5 Hz, 2H, H18), 3.27 – 3.21 (m, 2H, H7);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta_{\text{C}}$  150.8, 145.7, 144.8, 143.9, 137.7, 137.3, 137.3, 132.4, 124.5, 121.2, 120.6, 118.6, 116.3, 115.9, 115.7, 113.0, 56.1, 40.1, 39.6; HRMS (ESI+) calc. for  $\text{C}_{19}\text{H}_{20}\text{O}_3\text{Na}$   $[\text{M}+\text{Na}]^+$  319.1305, found 319.1305.

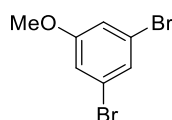
#### 4-Allyl-1-(5-allyl-2-((4-methoxybenzyl)oxy)phenoxy)-2-methoxybenzene, **24**



**24** was prepared according to general method G, using 4-allyl-2-(4-allyl-2-methoxyphenoxy)phenol (**23**, 50 mg, 0.17 mmol, 1.0 eq), *para*-methoxybenzyl chloride (28  $\mu$ L, 0.20 mmol, 1.2 eq), potassium carbonate (58 mg, 0.42 mmol, 2.5 eq) and DMF (1.3 mL). The reaction was complete after 90 minutes. The crude residue was purified by flash column chromatography (pentane / ethyl acetate (1 : 0  $\rightarrow$  9 : 1)) to afford **24** (61 mg, 0.15 mmol, 87%) as a colourless oil;  $R_f$  0.69 (pentane / ethyl acetate (4 : 1)); IR (neat,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3075, 2915, 1612, 1505, 1463, 1421, 1247, 1211, 1129, 1033;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$  7.20 – 7.10 (m, 2H, H22), 6.91 (d,  $J = 8.2$  Hz, 1H, H1), 6.86 – 6.78 (m, 5H, H23, H2, H14), 6.74 – 6.63 (m, 2H, H12, H4), 6.07 – 5.83 (m, 2H, H8, H17), 5.16 – 4.96 (m, 6H, H9, H18, H20), 3.83 (s, 3H, H19), 3.79 (s, 3H, H25), 3.38 (dt,  $J = 6.7, 1.5$  Hz, 2H, H16), 3.27 (dt,  $J = 6.7, 1.6$  Hz, 2H, H7);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta_{\text{C}}$  159.3, 150.2, 148.2, 146.6, 145.4, 137.7, 137.6, 135.3, 133.7, 129.6, 129.0, 124.0, 120.8, 120.7, 118.0, 115.9, 115.9, 115.8, 113.8, 113.3, 71.2, 56.2, 55.4, 40.1, 39.5; HRMS (ESI+) calc. for  $\text{C}_{27}\text{H}_{28}\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$  439.1880, found 439.1879.

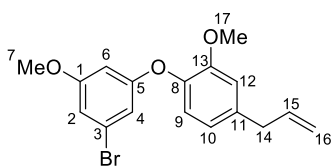


#### 5-Methoxy-1,3-dibromobenzene, **42**



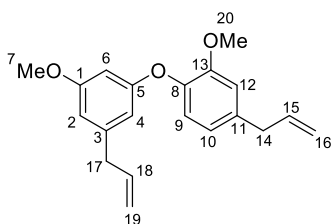
Methyl iodide (2.80 g, 19.8 mmol, 10.0 eq) was added to a mixture of 3,5-dibromophenol (0.50 g, 1.98 mmol, 1.0 eq) and potassium carbonate (2.2 g, 15.8 mmol, 8.0 eq) in ethanol (85 mL). The mixture was stirred under reflux for 12 h under argon atmosphere. The resulted mixture was evaporated *in vacuo* and poured into water. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and brine three times respectively, dried over anhydrous  $\text{MgSO}_4$ , then filtered and concentrated *in vacuo* to give **42** (490 mg, 1.84 mmol, 95%) as a white solid; MP 38 – 39  $^\circ\text{C}$ ;  $R_f$  0.57 (petrol / EtOAc (9 : 1));  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.26 (t,  $J = 1.5$  Hz, 1H), 7.00 (d,  $J = 1.5$  Hz, 2H), 3.80 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  161.0, 126.6, 123.2, 116.6, 55.9. The experimental data is in good agreement with that described in the literature.<sup>14</sup>

#### 4-Allyl-1-(3-bromo-5-methoxyphenoxy)-2-methoxybenzene, **43**



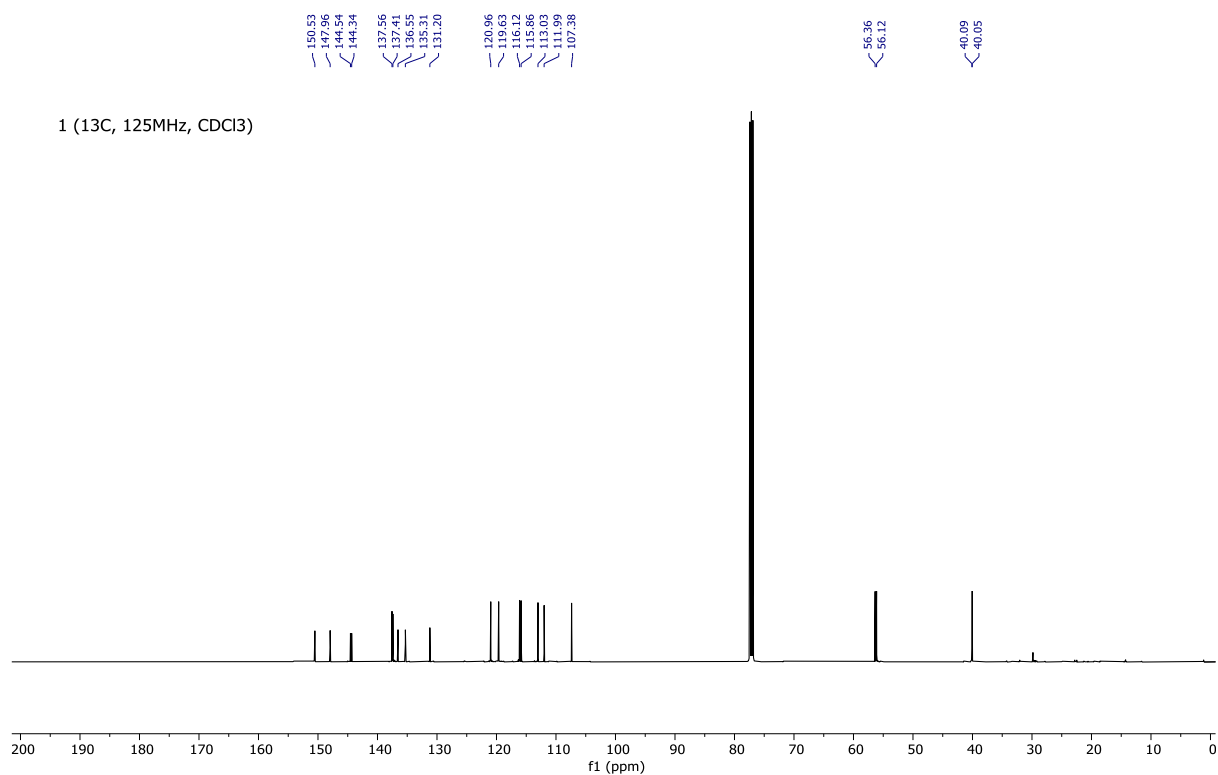
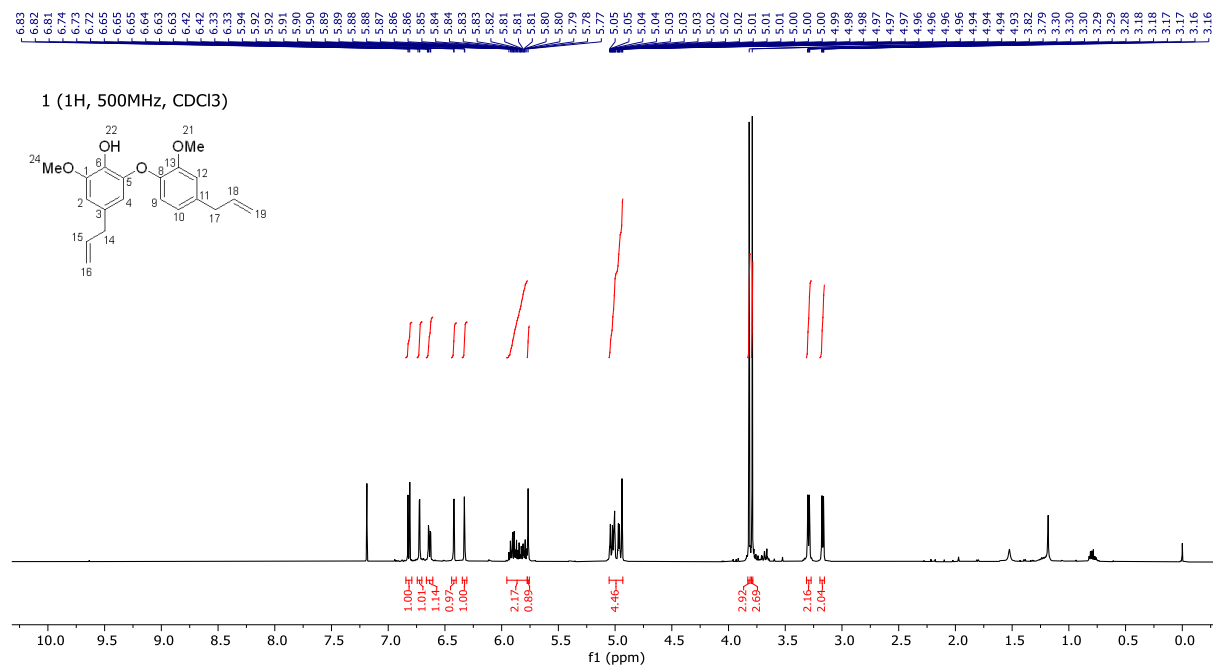
**43** was prepared according to general method D using 5-methoxy-1,3-dibromobenzene (**42**, 800 mg, 3.03 mmol, 2.0 eq), eugenol (**3**, 248mg, 1.51 mmol, 1.0 eq), copper(I) chloride (75 mg, 0.75 mmol, 0.5 eq), TMHD (158  $\mu$ L, 0.75 mmol, 0.5 eq), cesium carbonate (988 mg, 3.03 mmol, 2.0 eq), NMP (2.0 mL) and dioxane (4.0 mL). The reaction was complete after 24 hours. The crude residue was purified via flash column chromatography (petrol / EtOAc (1 : 0  $\rightarrow$  9 : 1)), to afford **43** (281 mg, 0.81 mmol, 53%) as colorless oil;  $R_f$  0.72 (petrol / EtOAc (9 : 1)); IR (thin film,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3080, 2943, 2838, 1600, 1502, 1261, 1212, 1118, 1033, 831, 712;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.94 (d,  $J = 8.0$  Hz, 1H), 6.82 (d,  $J = 1.9$  Hz, 1H), 6.77 (dd, 1H,  $J = 8.1$  Hz, 1.9 Hz), 6.72 (m, 1H), 6.60 (m, 1H), 6.43 (m, 1H), 5.99 (ddt,  $J = 16.9$ , 10.1, 6.7 Hz, 1H), 5.16-5.10 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.40 (d,  $J = 6.7$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  161.3, 160.3, 151.6, 141.9, 138.1, 137.3, 122.9, 122.2, 121.2, 116.3, 113.4, 112.2, 111.3, 102.1, 56.1, 55.7, 40.2; HRMS (ES+) calc. for  $\text{C}_{17}\text{H}_{17}\text{BrO}_3$   $[\text{M}+\text{H}]^+$  349.0439, found 349.0433.

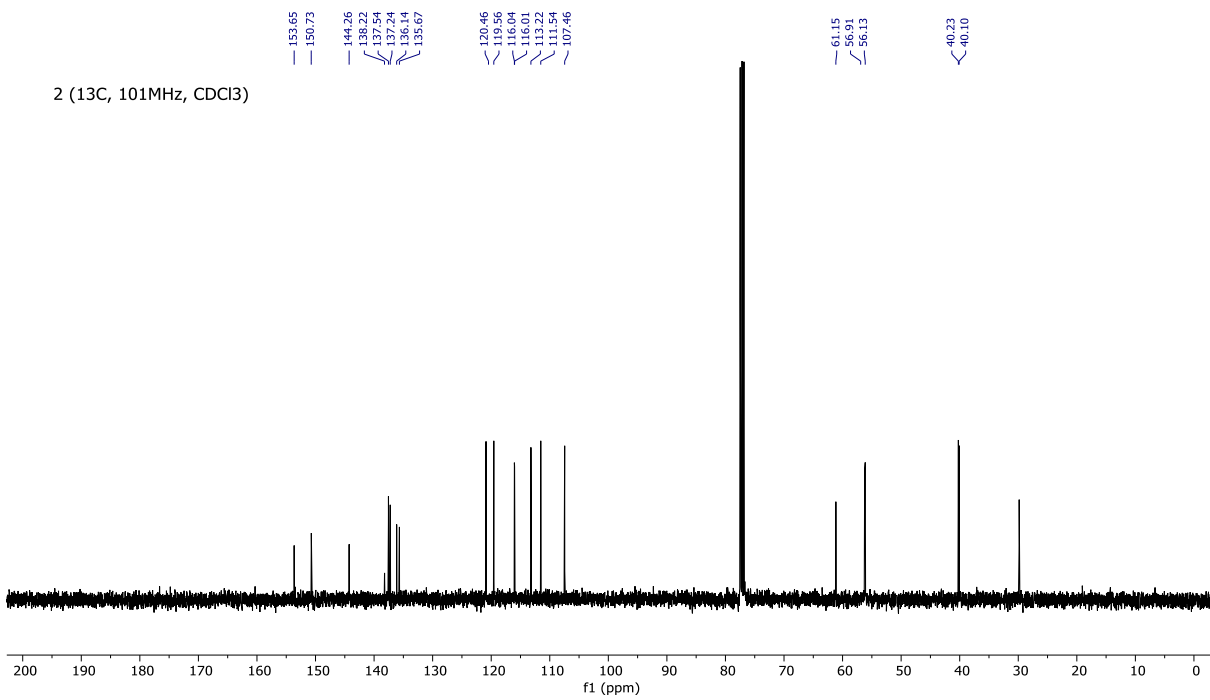
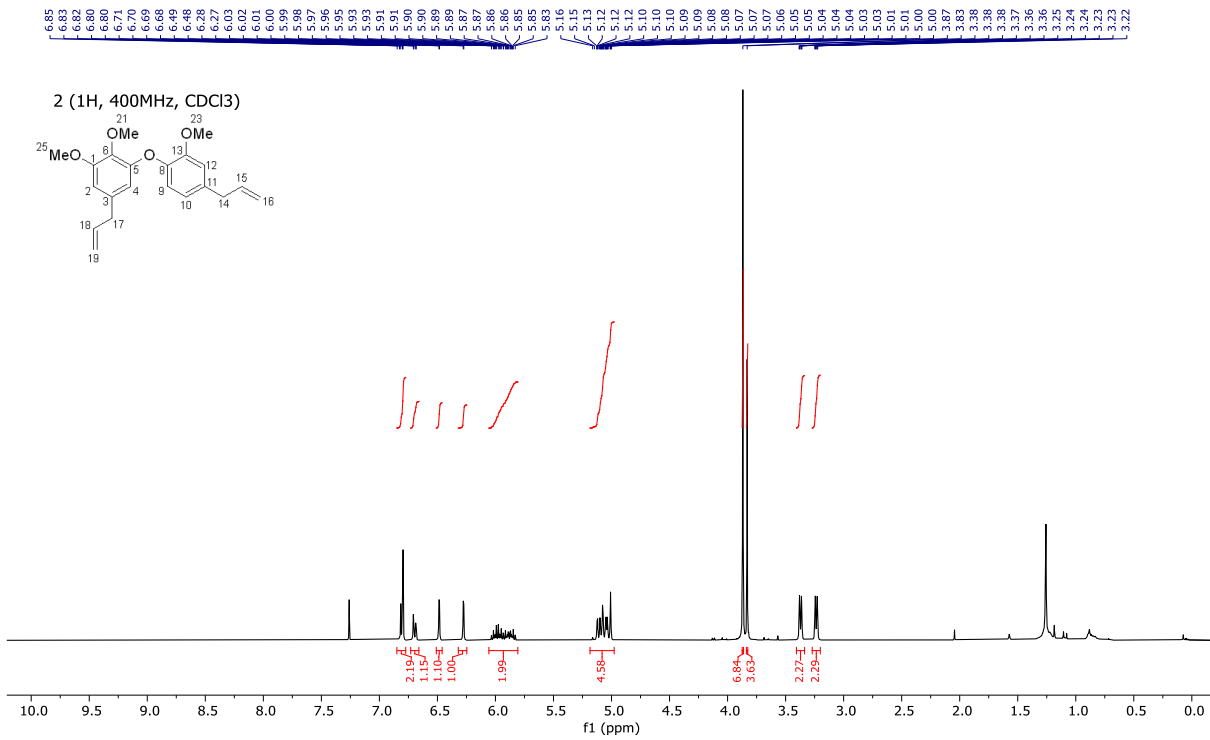
#### 4-Allyl-1-(3-allyl-5-methoxyphenoxy)-2-methoxybenzene, **25**

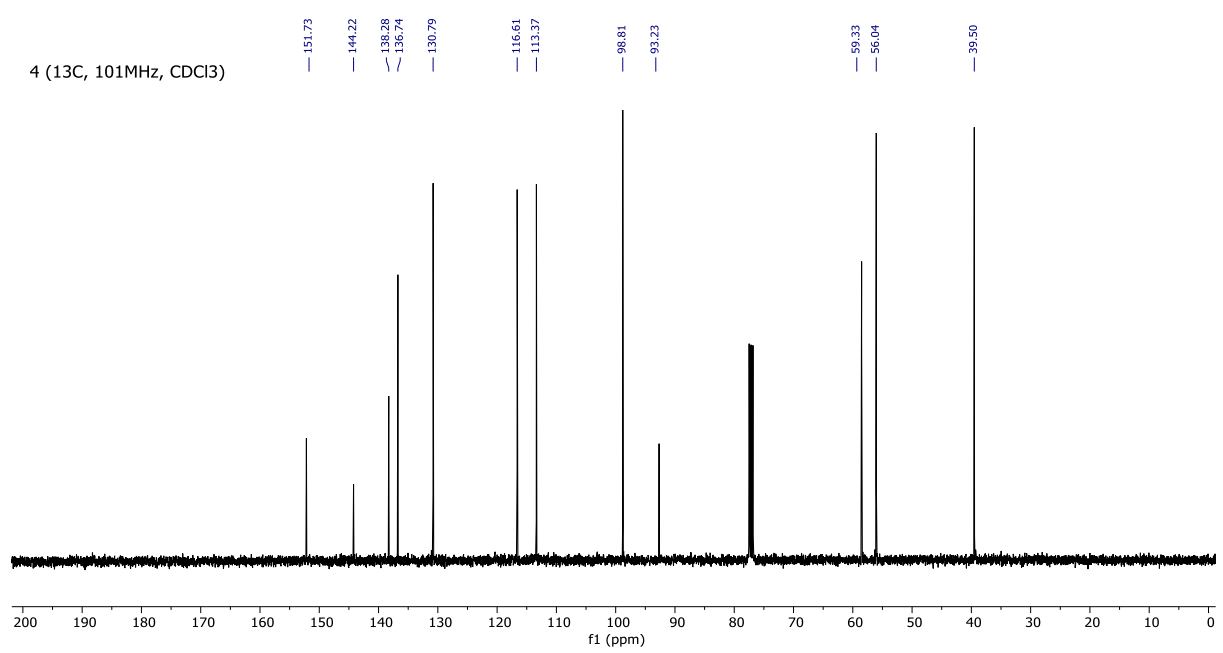
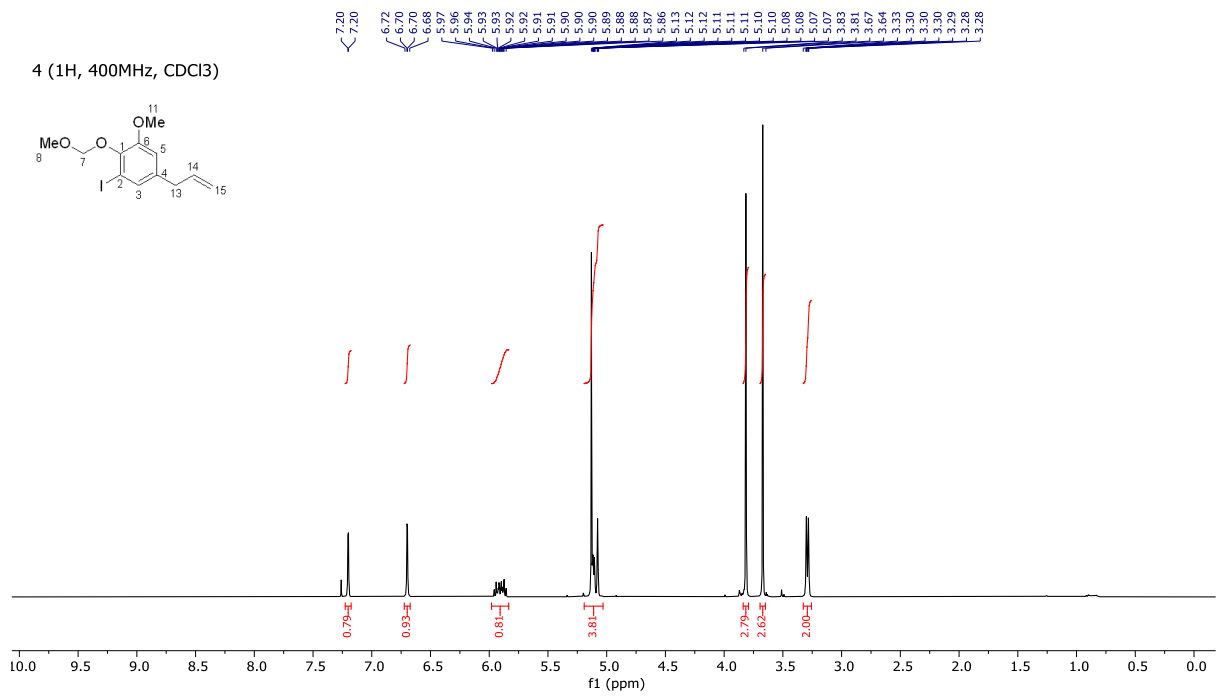


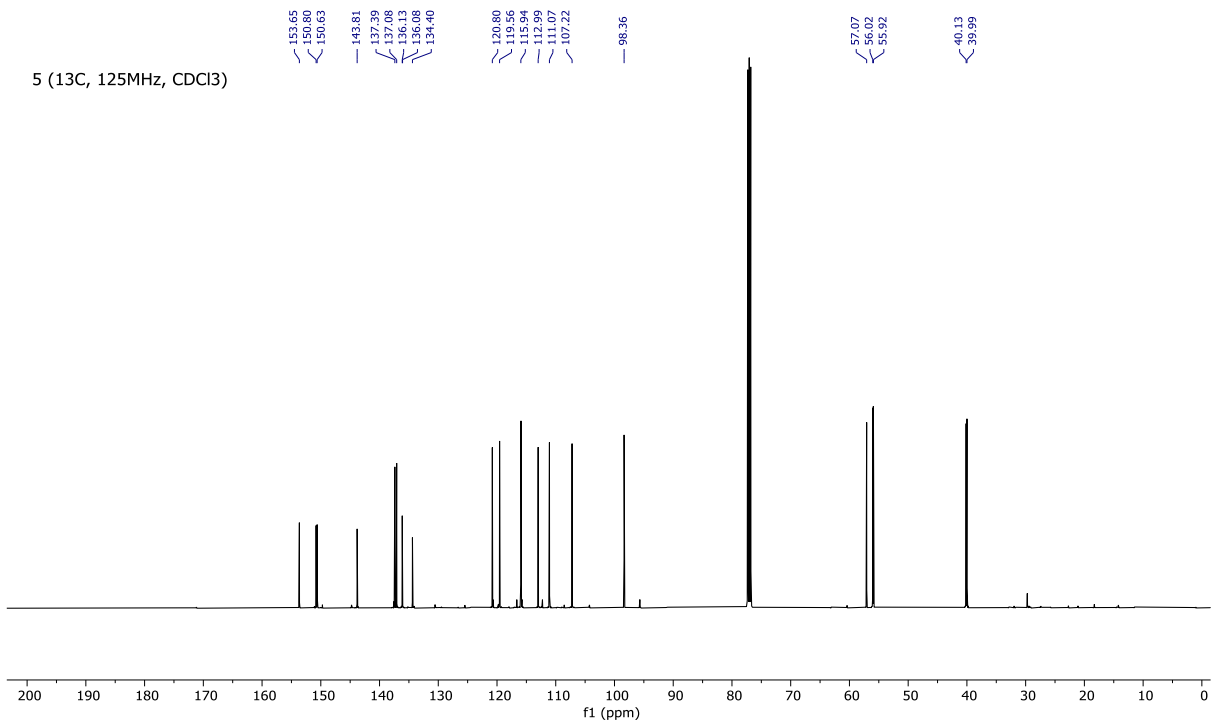
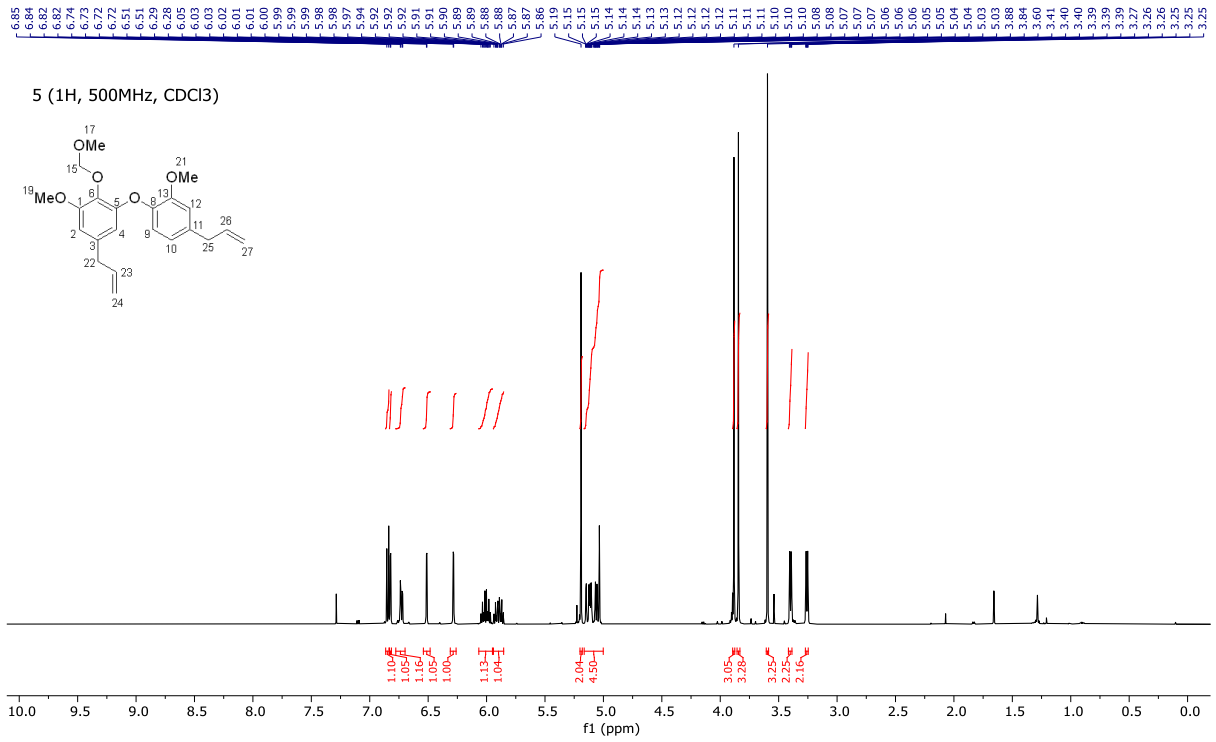
A flame-dried Schlenk flask was charged with  $\text{Pd}_2(\text{dba})_3$  (4.3 mg,  $4.7 \times 10^{-3}$  mmol, 0.5 mol%), BINAP (5.9 mg,  $9.5 \times 10^{-3}$  mmol, 1 mol%) and dioxane (3 mL). The resulting red solution was stirred for 30 minutes at room temperature after which time the 4-allyl-1-(3-bromo-5-methoxyphenoxy)-2-methoxybenzene (**43**, 330 mg, 0.95 mmol, 1.0 eq) was added, followed by allylmagnesium chloride (1.7 M in THF, 1.4 mL, 2.37 mmol, 2.5 eq), in a dropwise manner. The flask was fitted with a reflux condenser and heated at 80  $^\circ\text{C}$  for six hours. The resulting mixture was quenched by slow addition of 10% aqueous HCl (5 mL) and the product extracted into diethyl ether ( $3 \times 20$  mL). The organic phases were combined, dried over  $\text{MgSO}_4$  and the solvent removed to leave a yellow-brown oil, that was purified *via* flash column chromatography (petrol / EtOAc (1 : 0  $\rightarrow$  9 : 1)) to afford **25** (209 mg, 0.67 mmol, 71%) as a colorless oil;  $R_f$  0.62 (petrol / EtOAc (9 : 1)); IR (thin film,  $\nu_{\max}$  /  $\text{cm}^{-1}$ ) 3076, 3003, 2936, 2836, 2360, 1638, 1589, 1506, 1463, 1432, 1266, 1212, 1190, 1151, 1134, 1058, 1035;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  6.91 (d,  $J = 8.1$  Hz, 1H), 6.81 (d,  $J = 1.9$  Hz, 1H), 6.74 (dd,  $J = 8.1$ , 2.0 Hz, 1H), 6.41 (d,  $J = 14.9$  Hz, 2H), 6.33 (t,  $J = 2.3$  Hz, 1H), 6.04 – 5.87 (m, 2H), 5.20 – 4.95 (m, 4H), 3.82 (s, 3H), 3.74 (s, 3H), 3.39 (d,  $J = 6.7$ , 2H), 3.29 (d,  $J = 6.7$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  160.9, 159.5, 151.5, 148.6, 143.1, 142.7, 137.4, 137.1, 121.3, 121.1, 116.2, 116.2, 113.3, 109.8, 108.4, 101.0, 56.1, 55.5, 40.4, 40.2; HRMS (ESI+) calc. for  $\text{C}_{20}\text{H}_{23}\text{O}_3$   $[\text{M}+\text{H}]^+$  311.1641, found 311.1642.

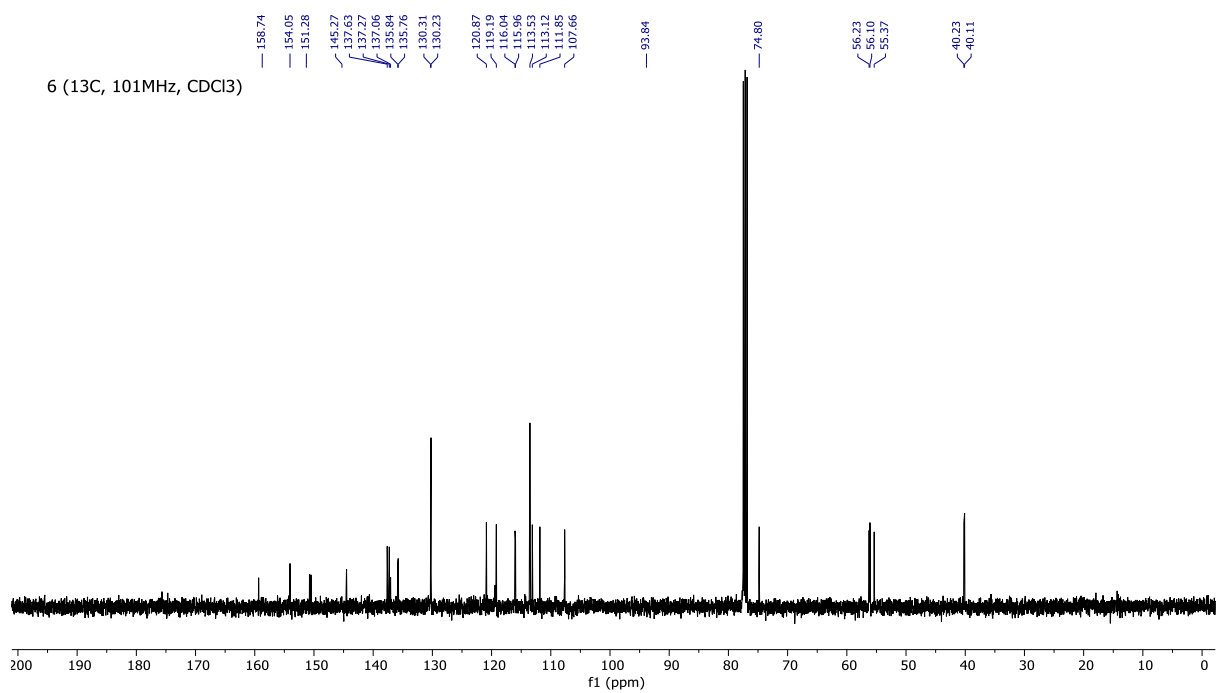
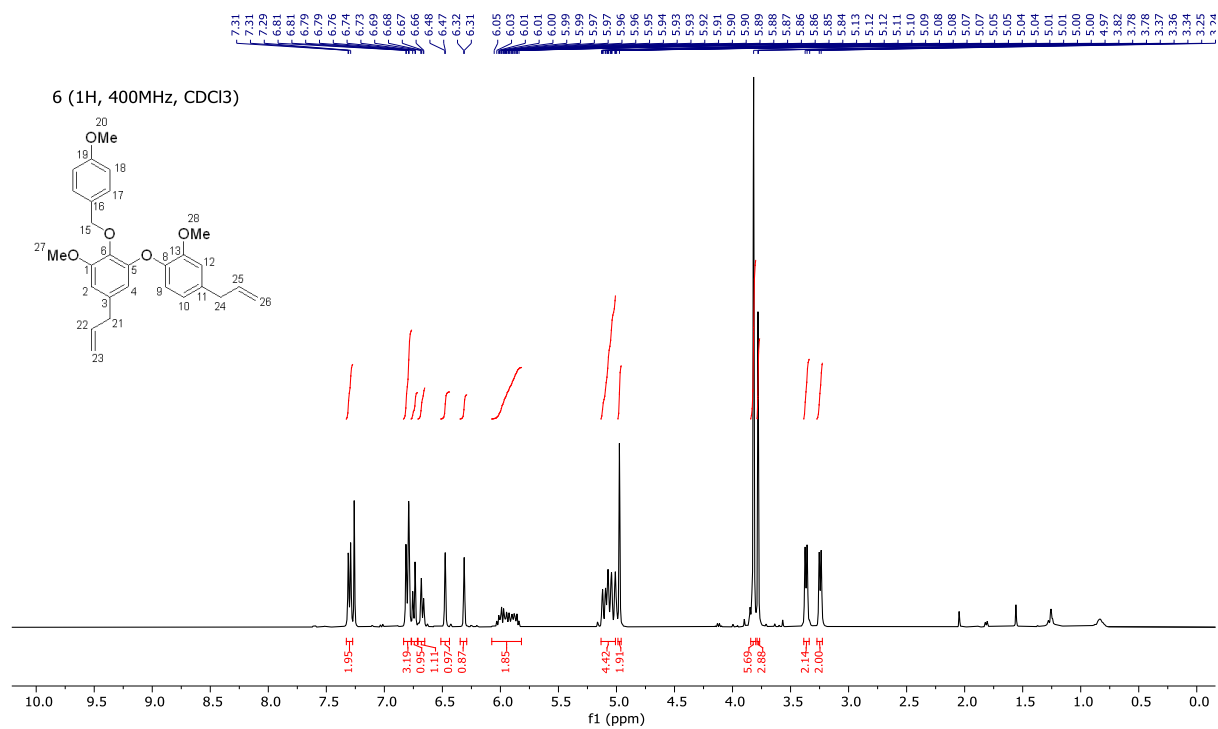
## 4. Copies of <sup>1</sup>H and <sup>13</sup>C NMR Spectra

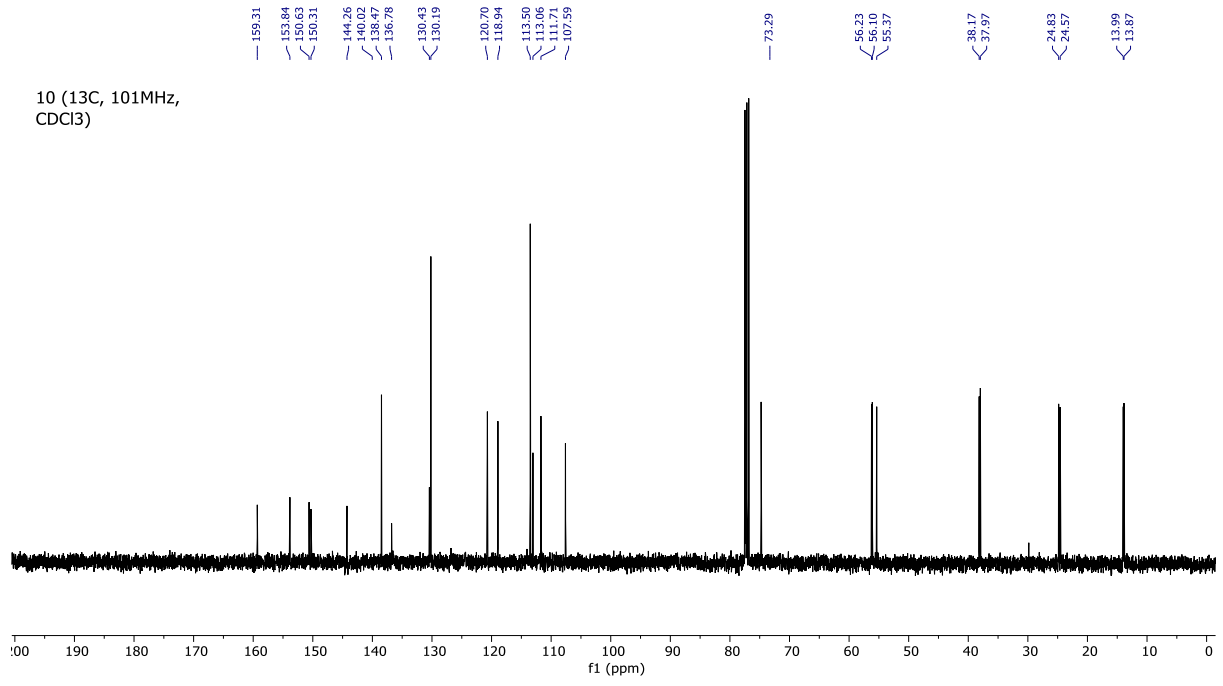
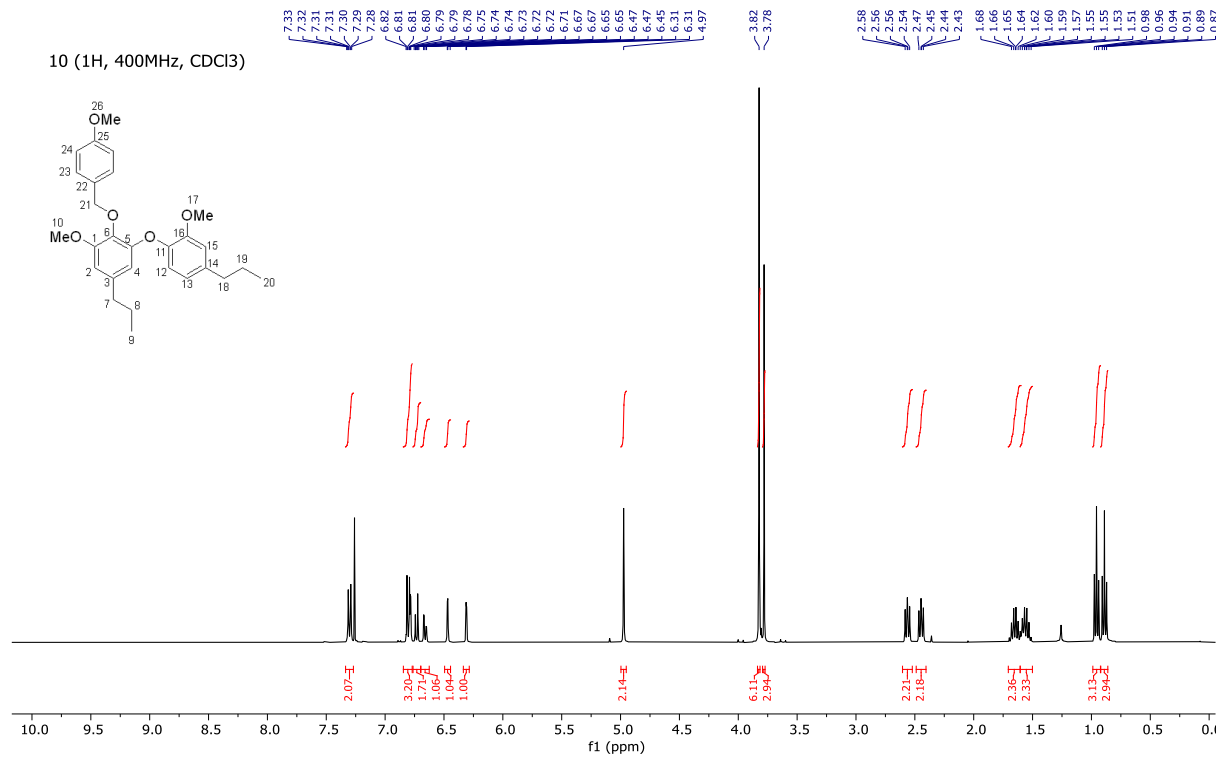


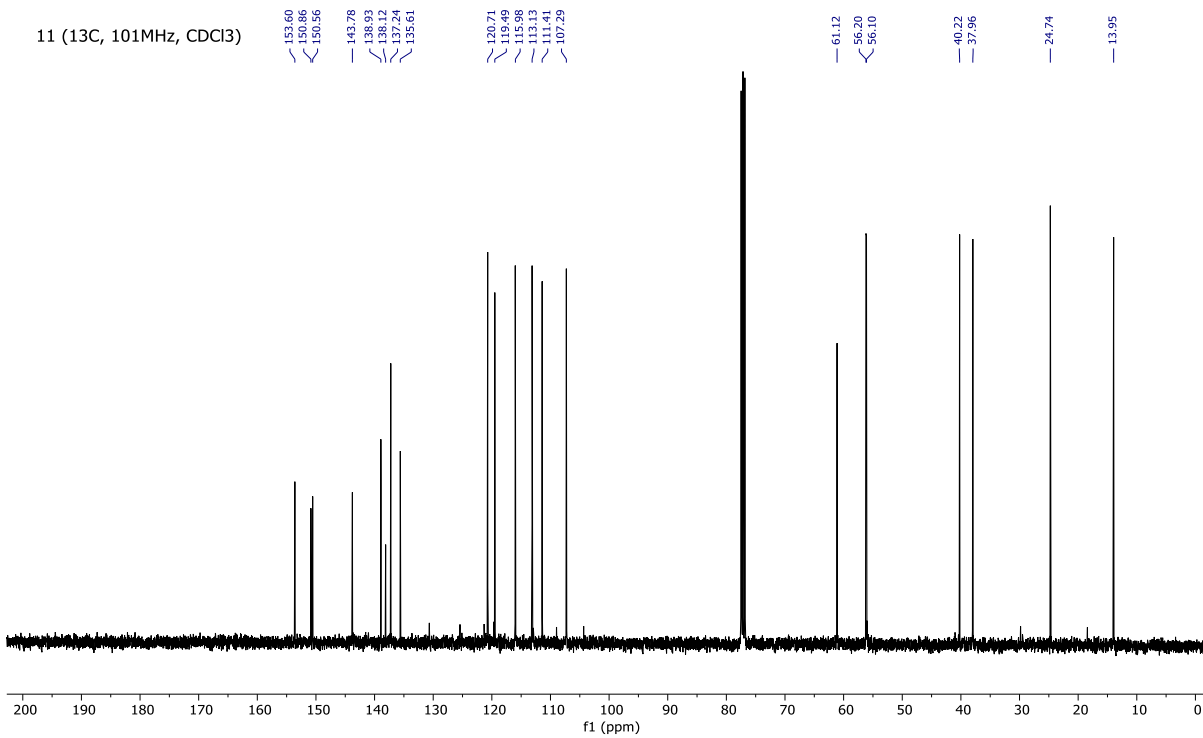
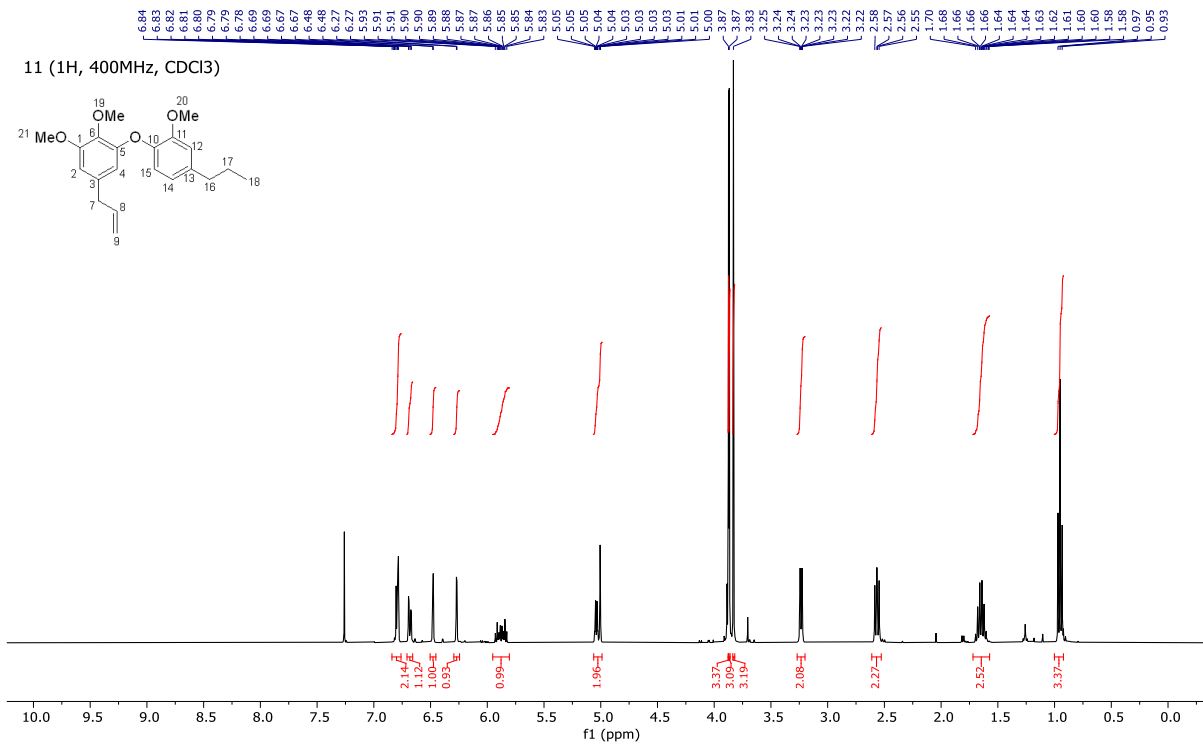


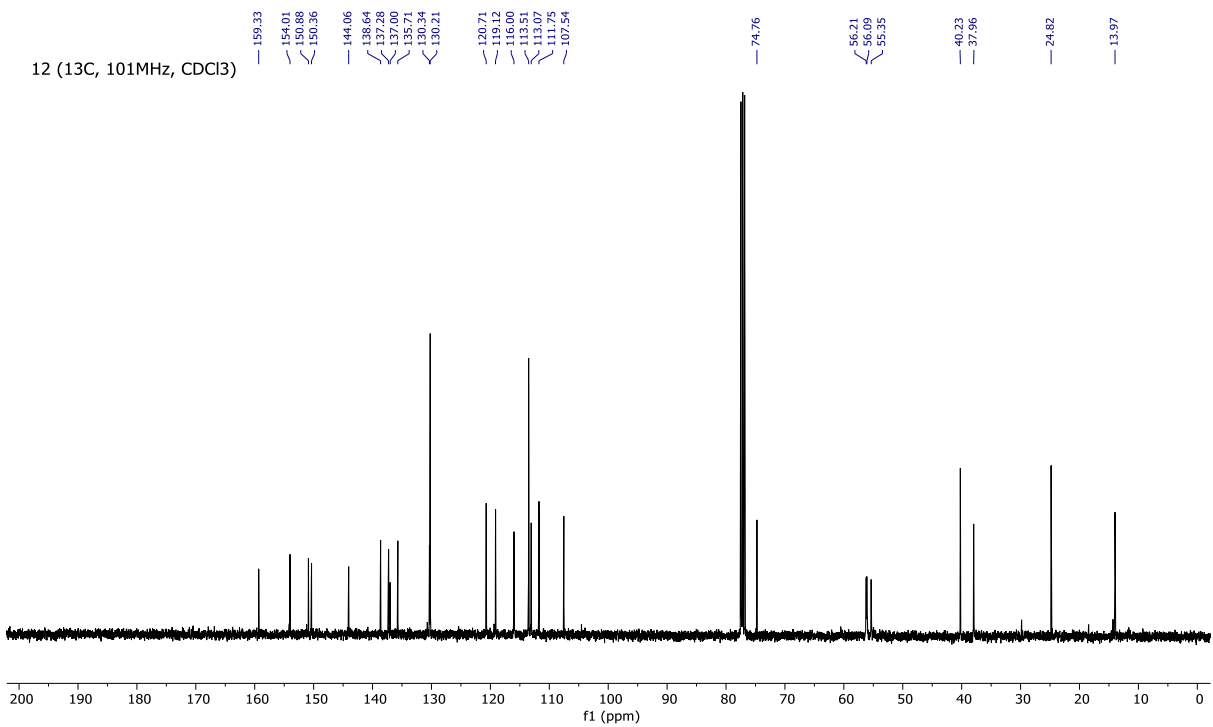
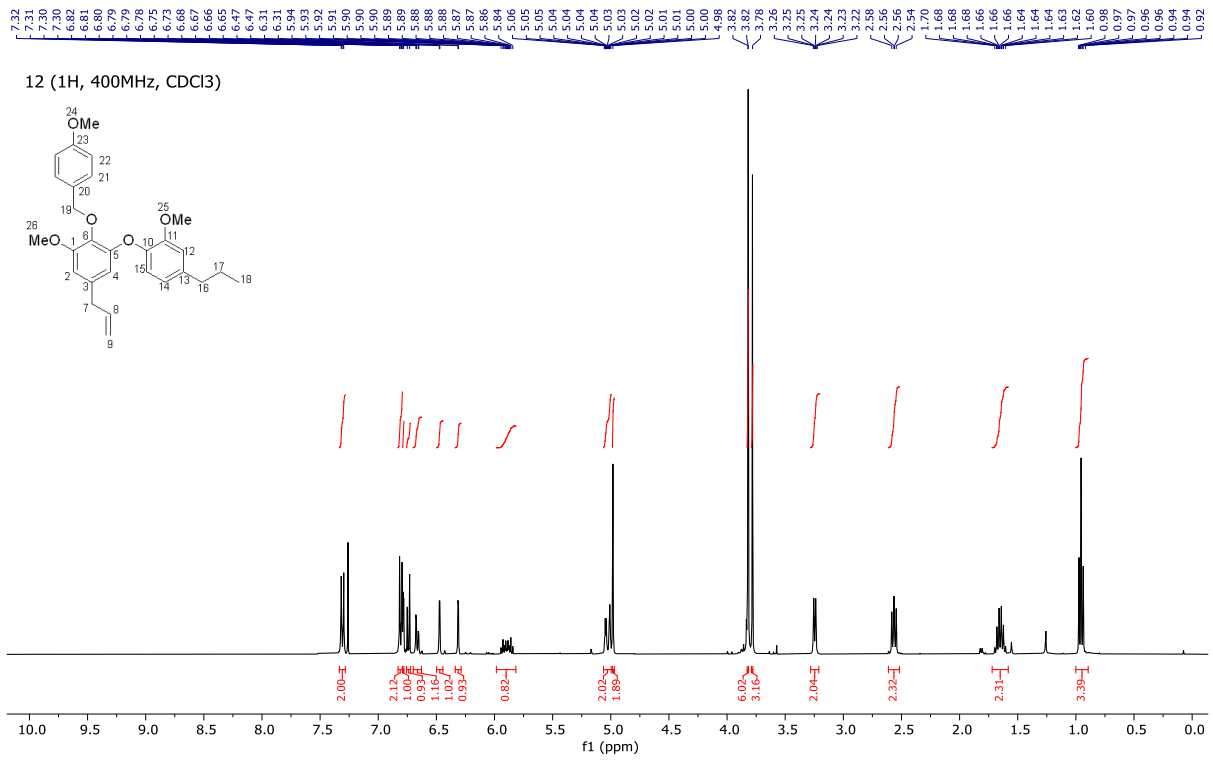




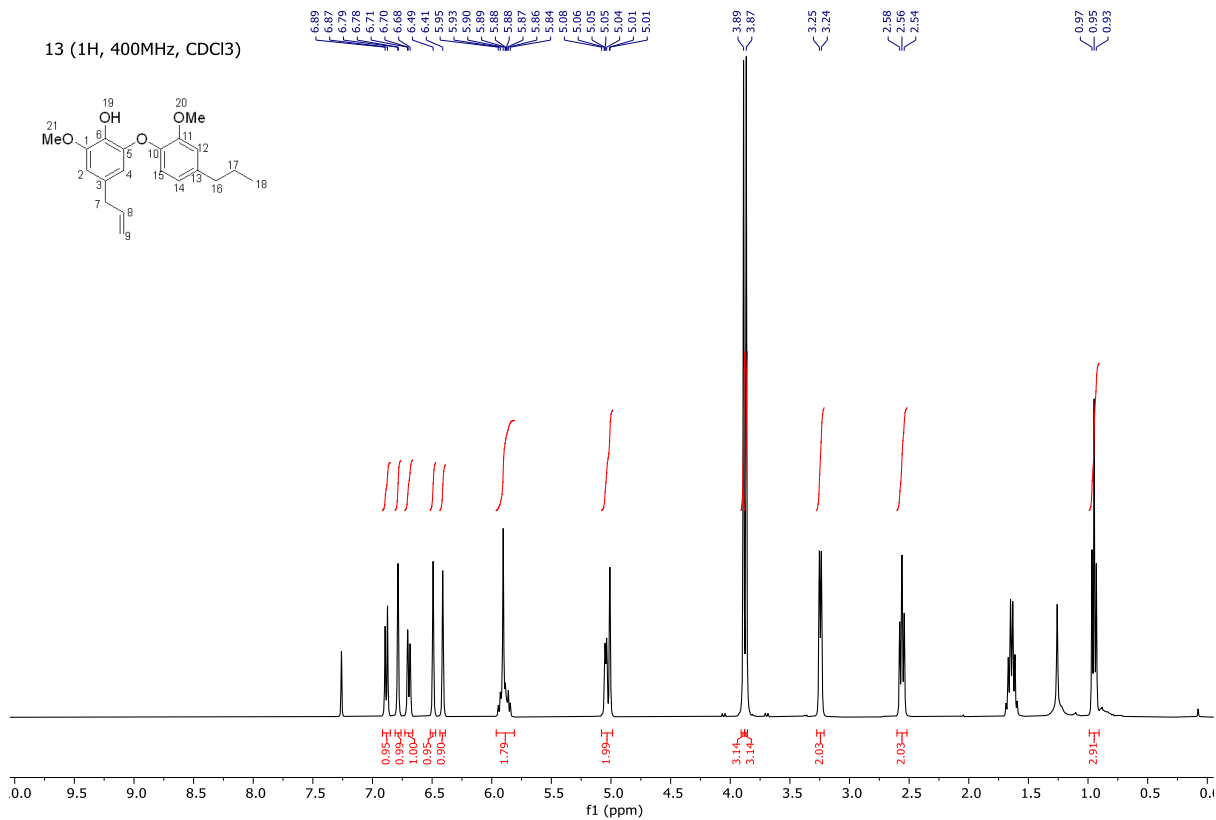
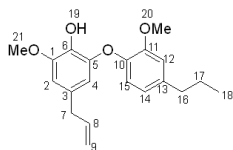




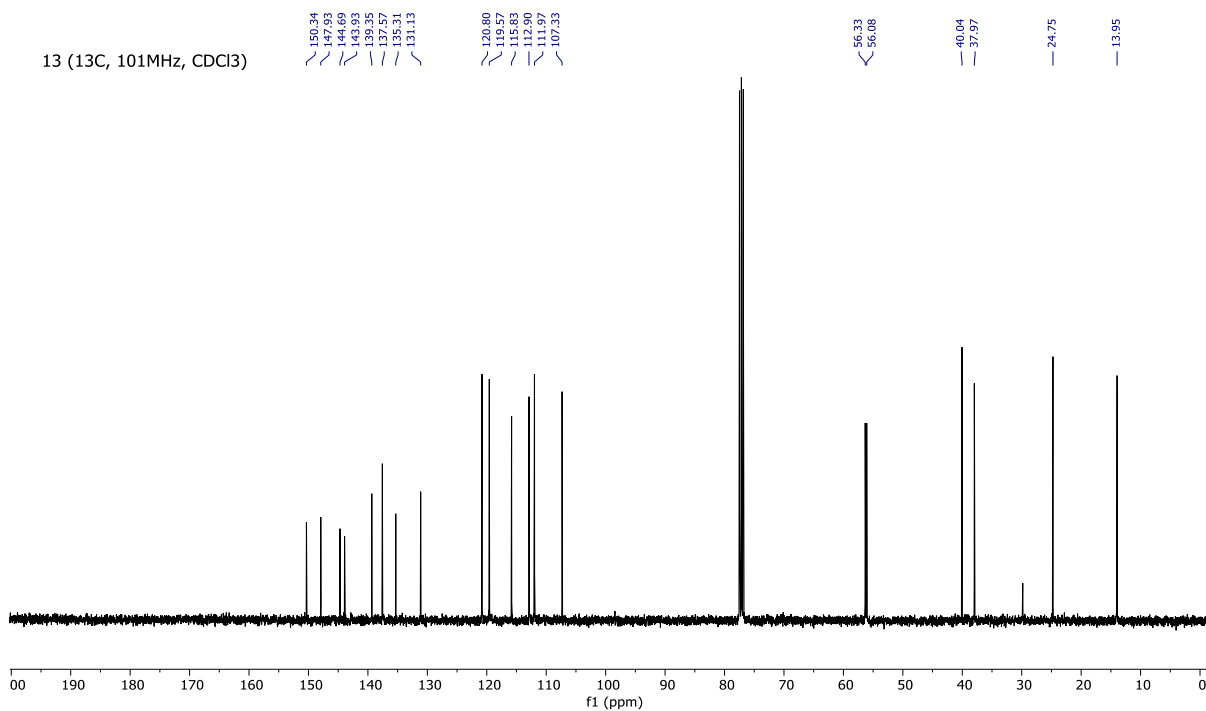


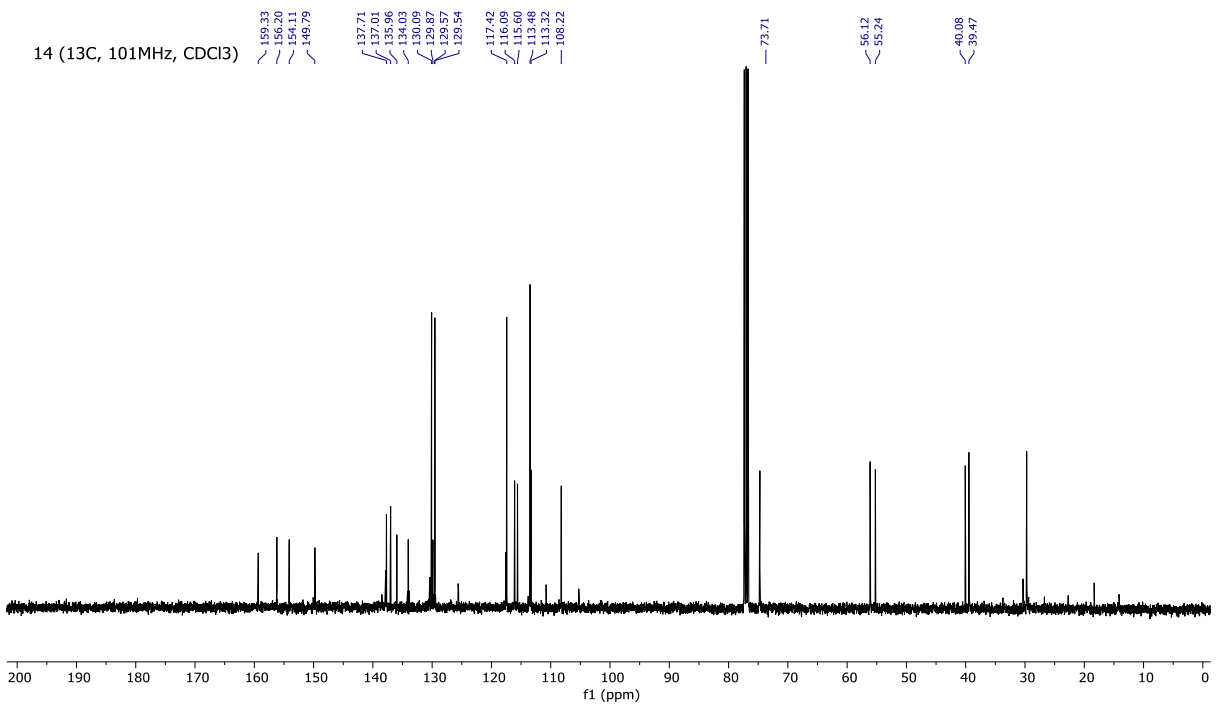
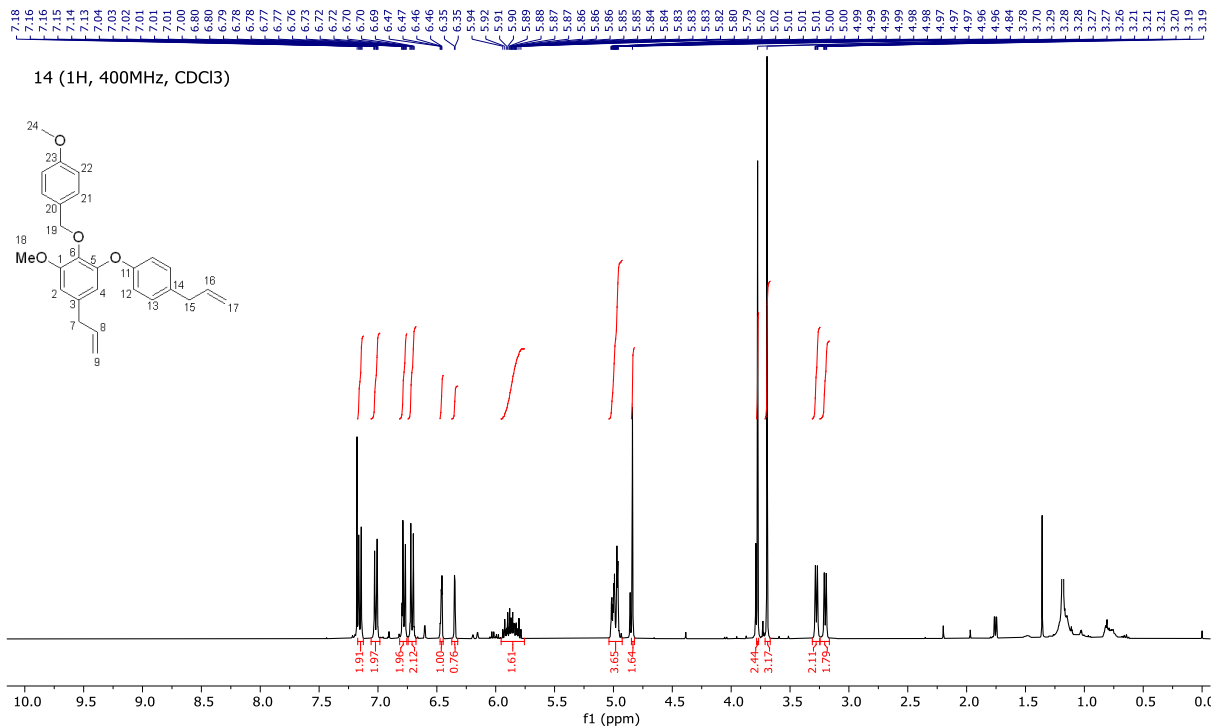


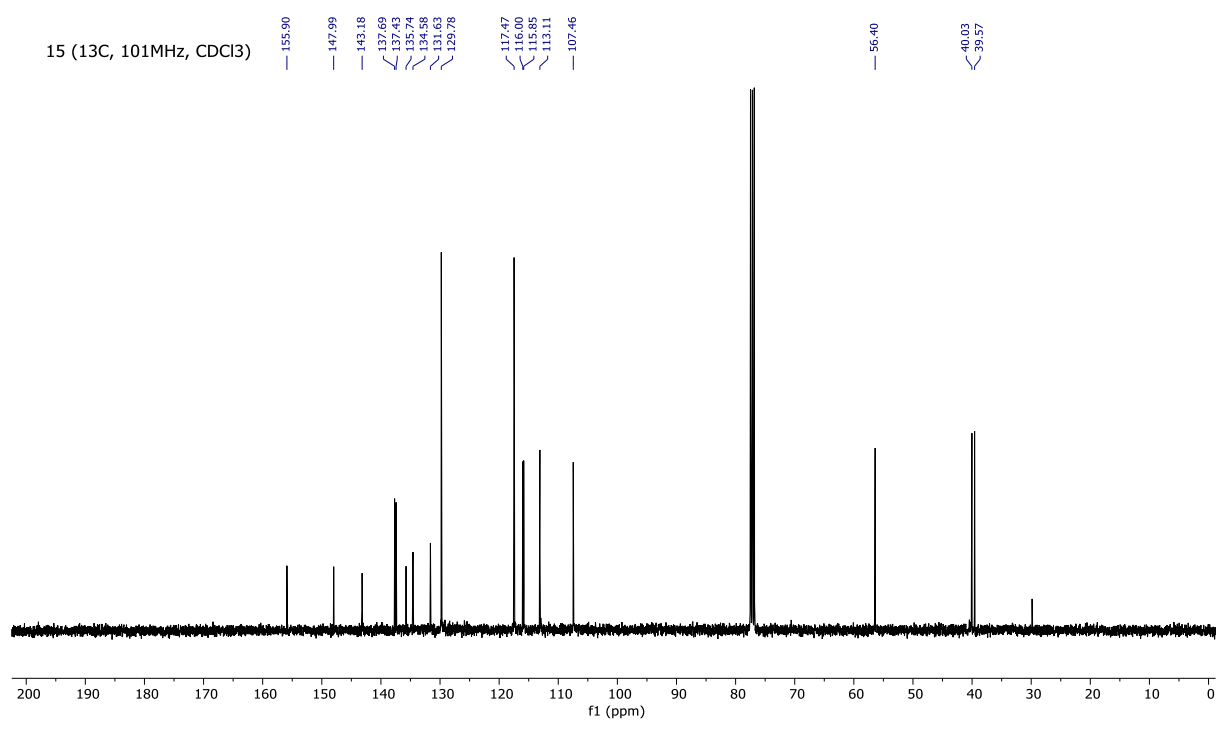
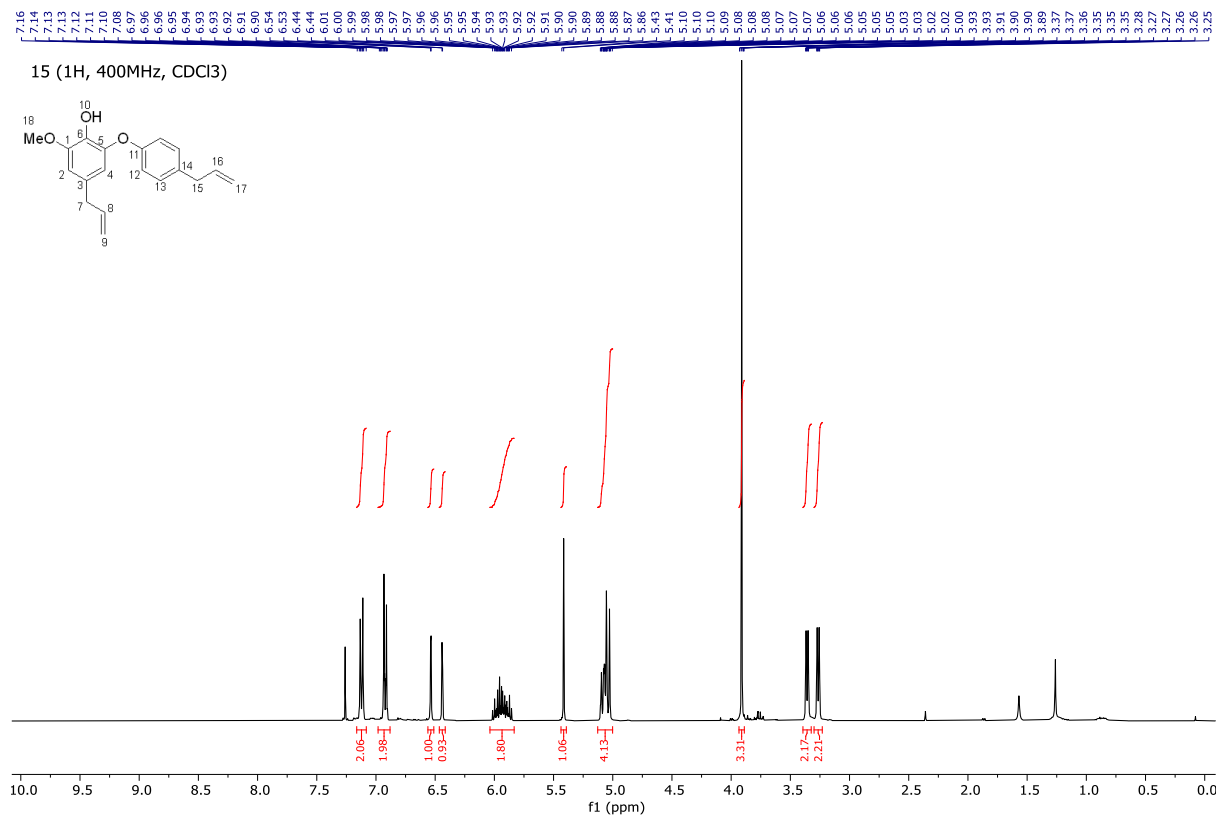
13 (1H, 400MHz, CDCl3)



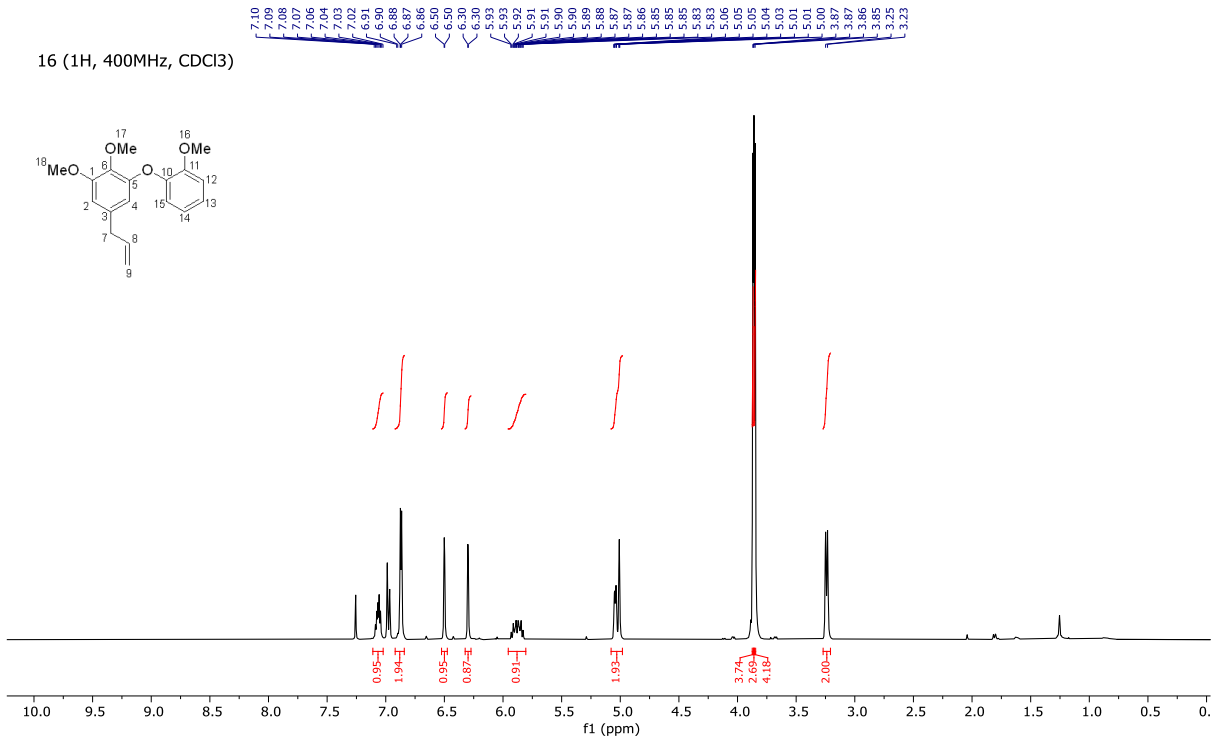
13 (13C, 101MHz, CDCl3)



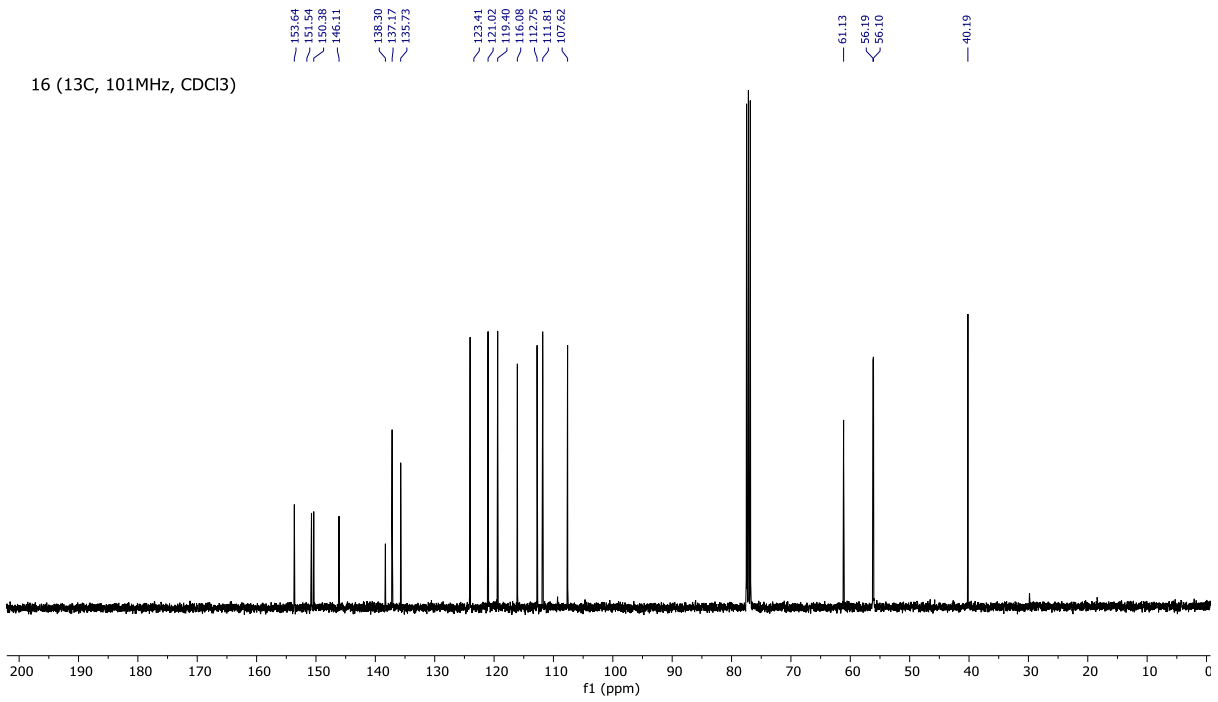


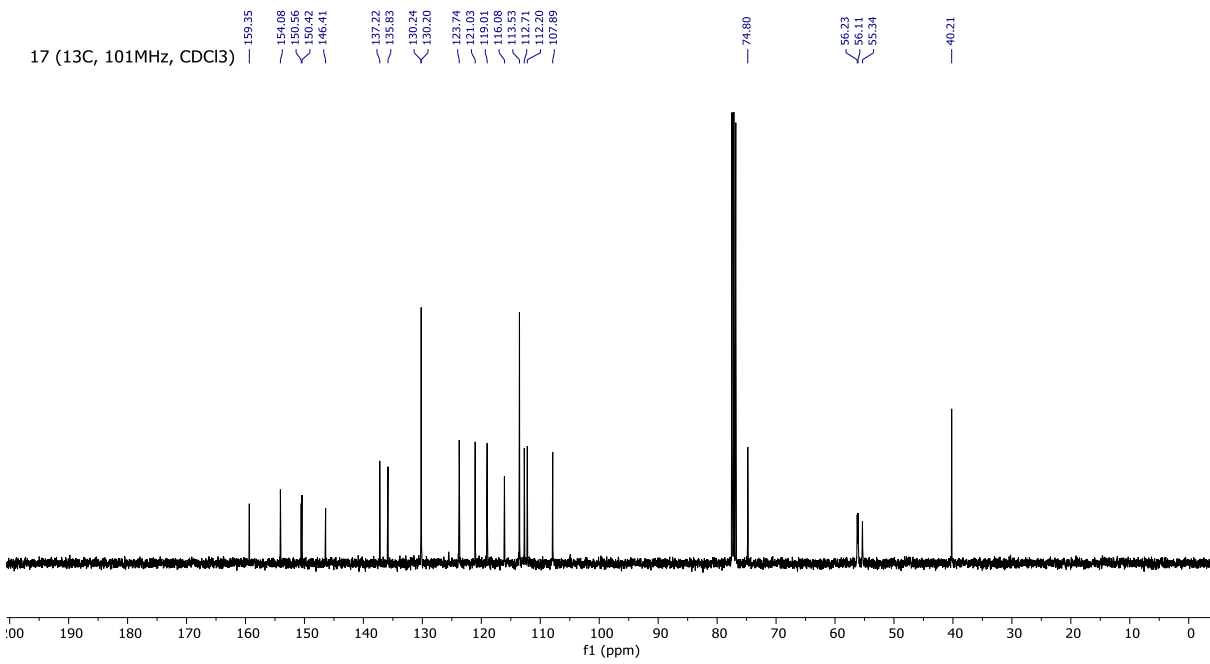
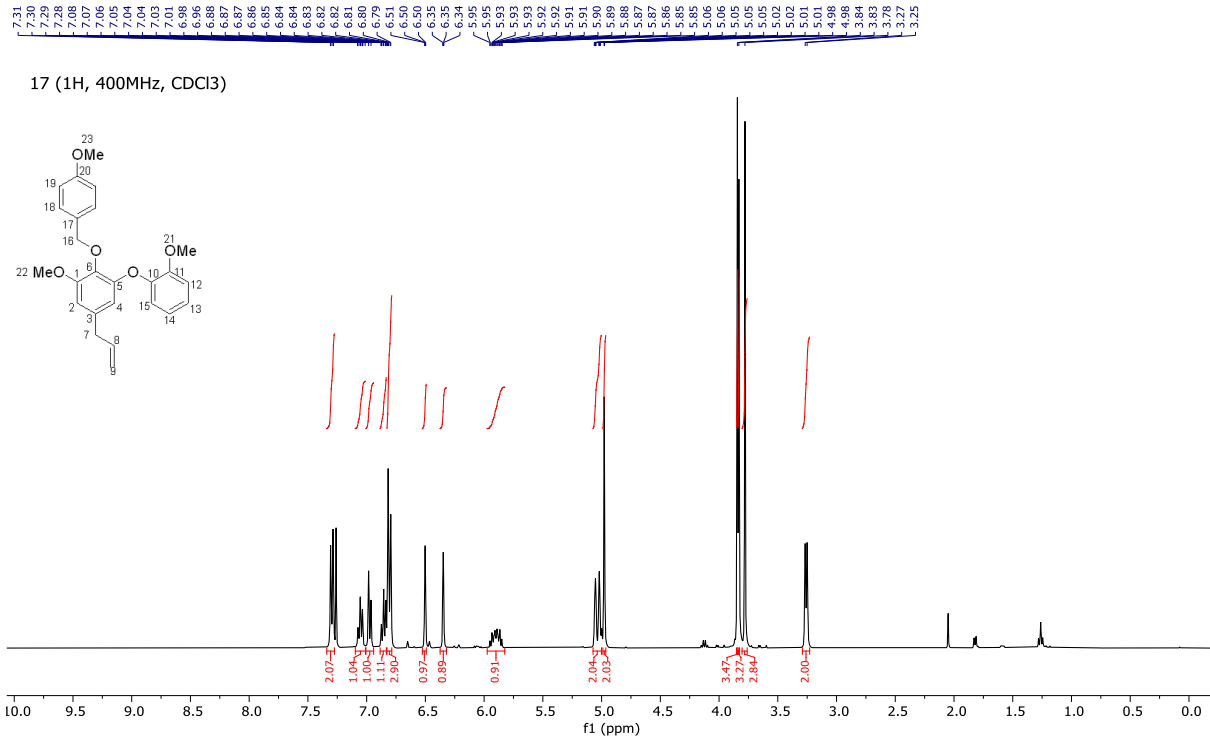


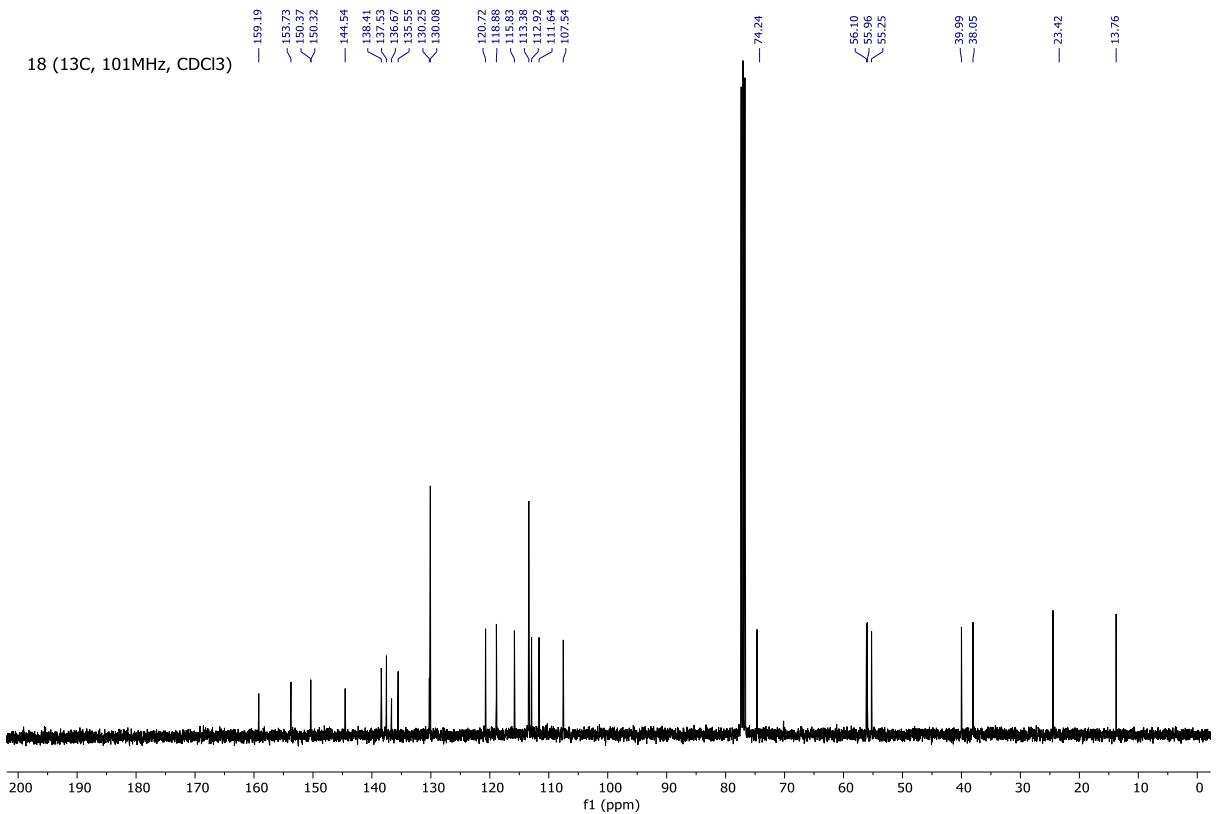
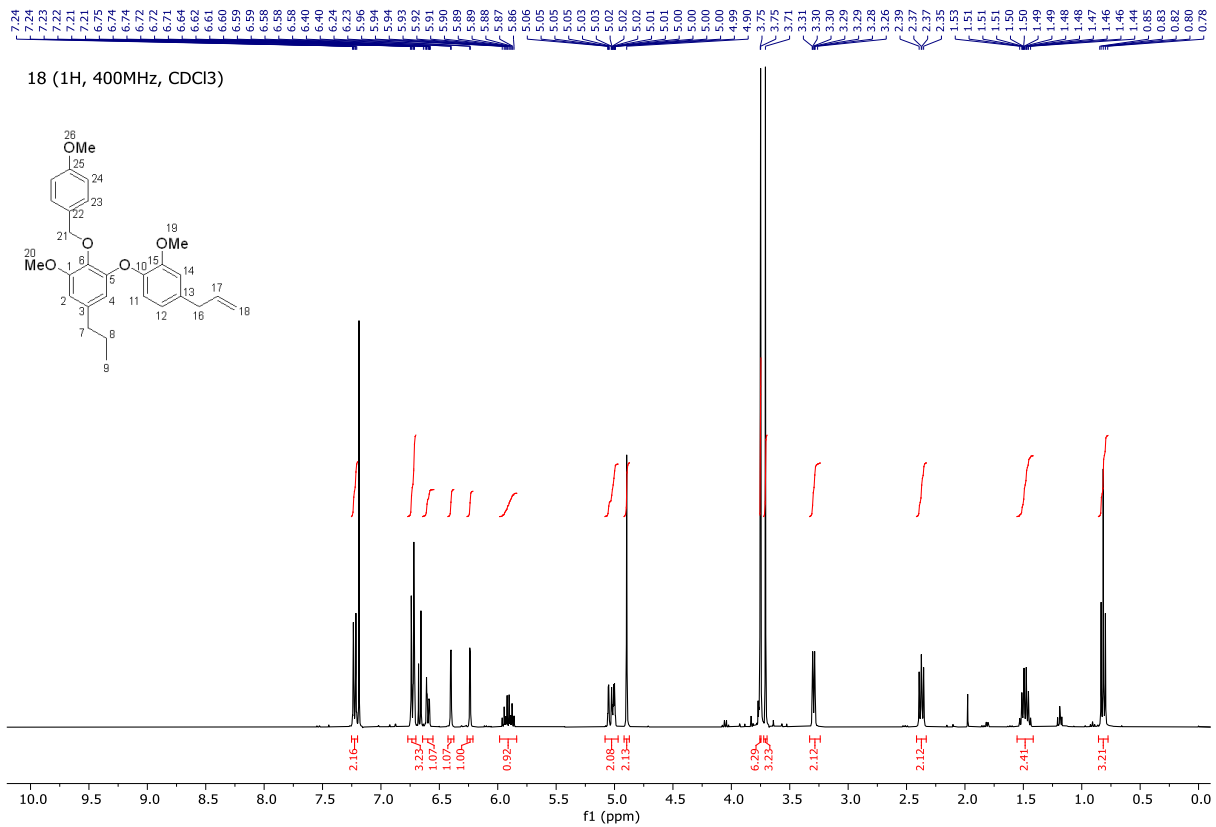
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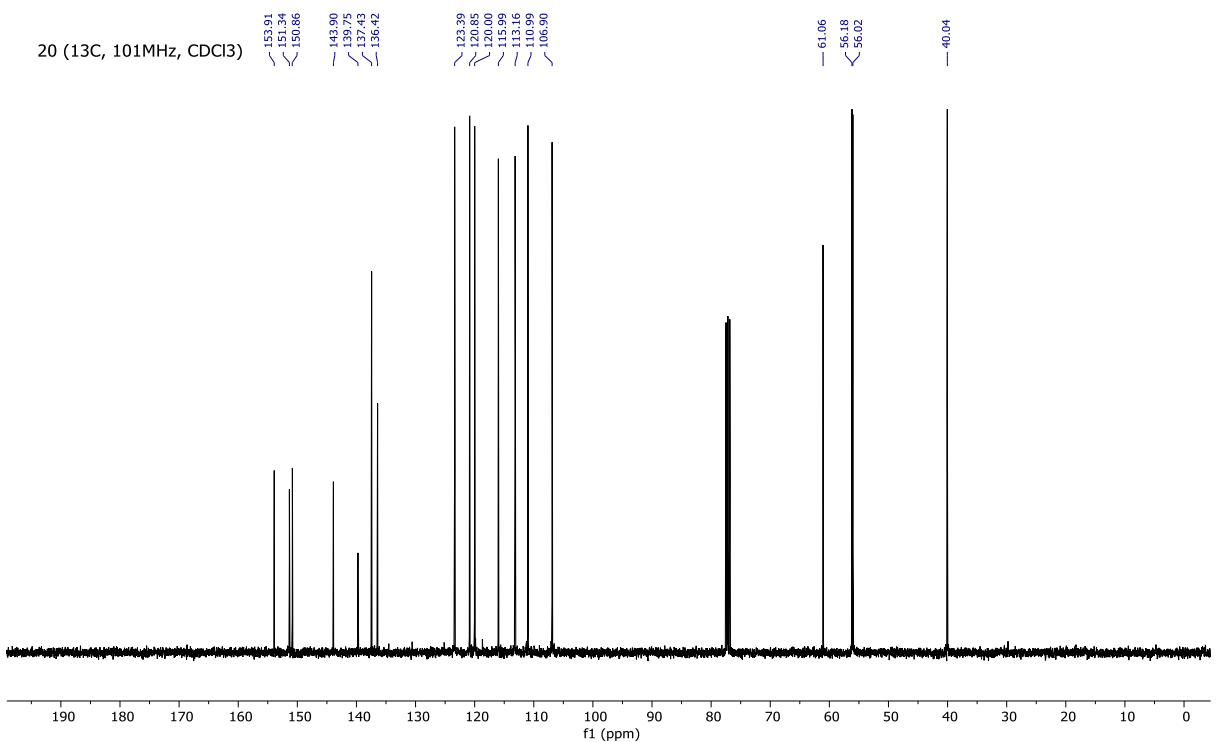
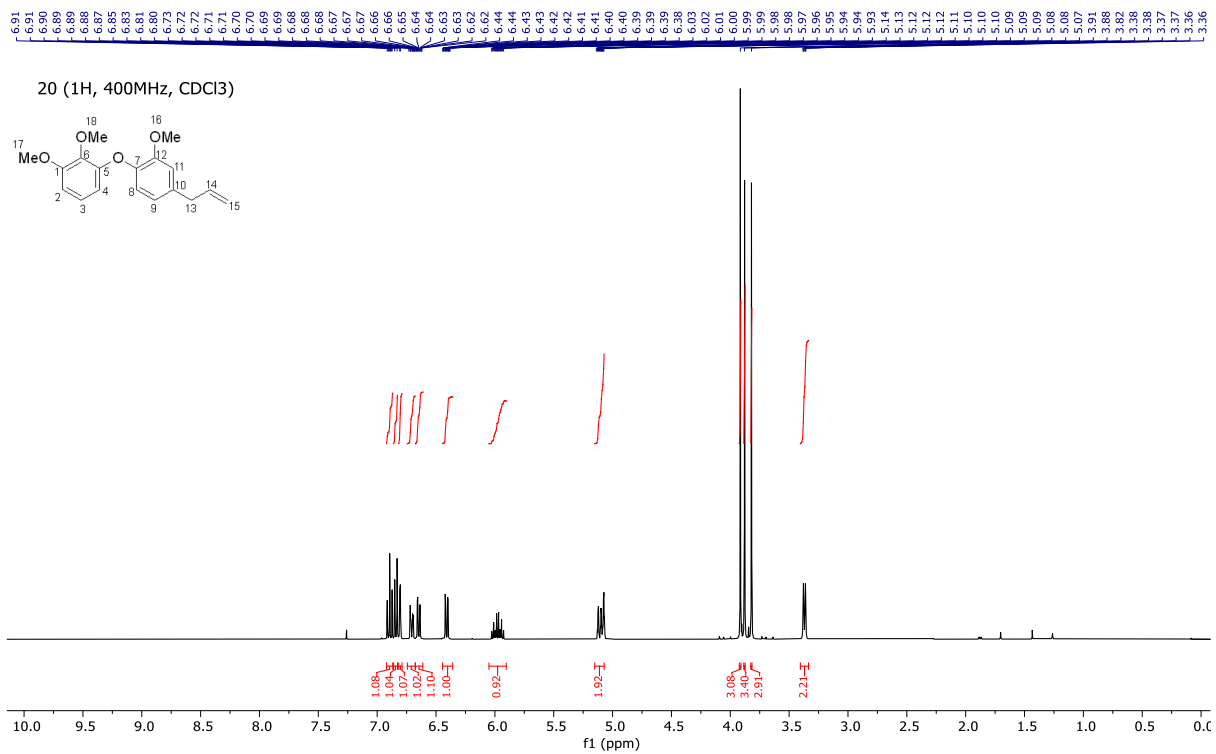
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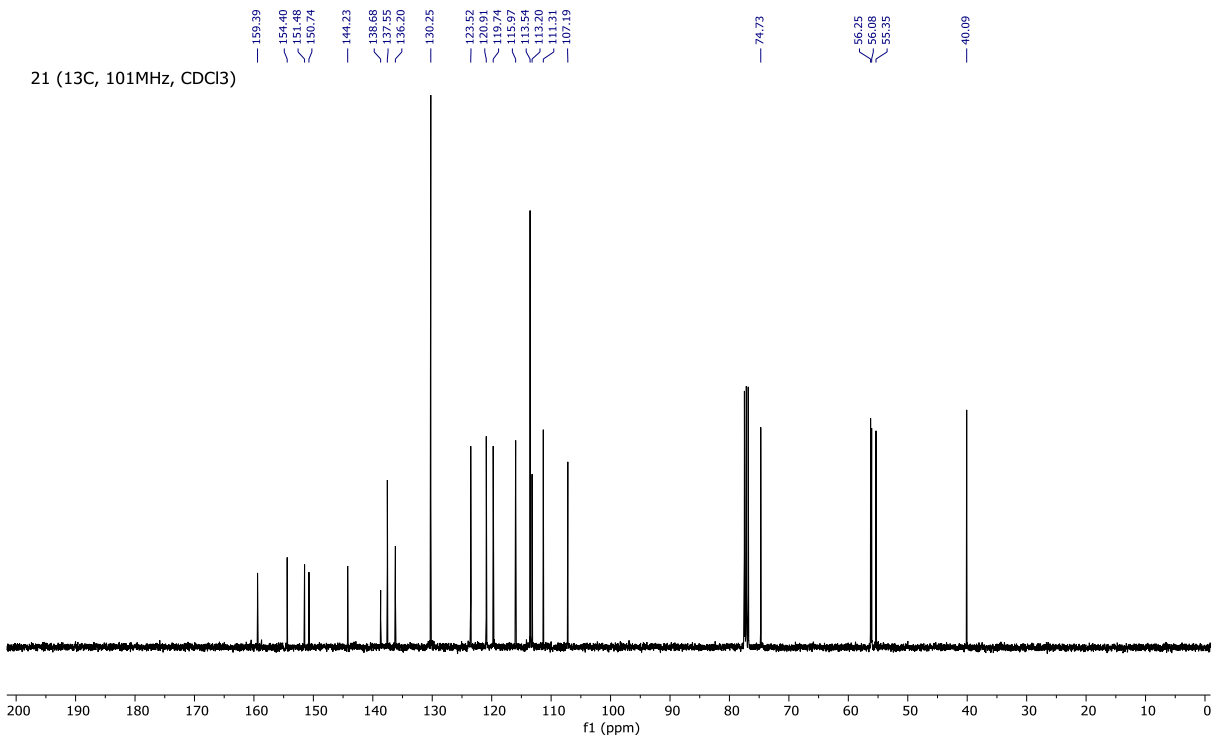
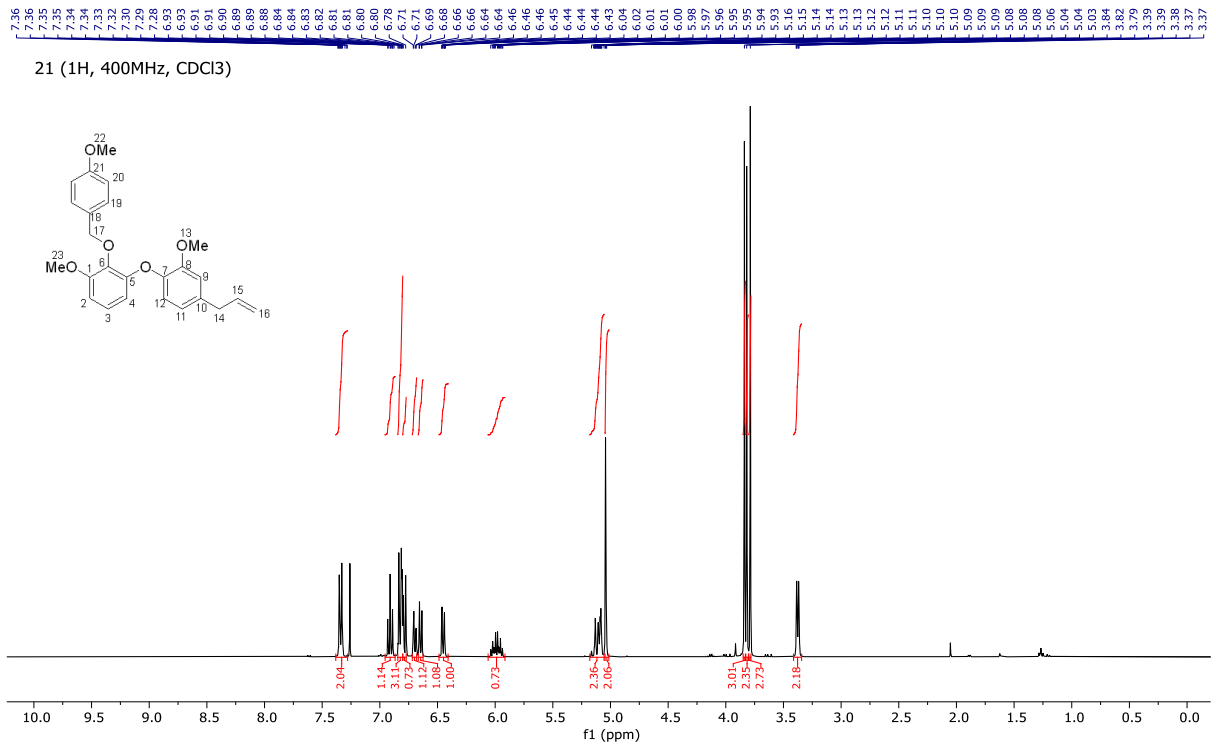


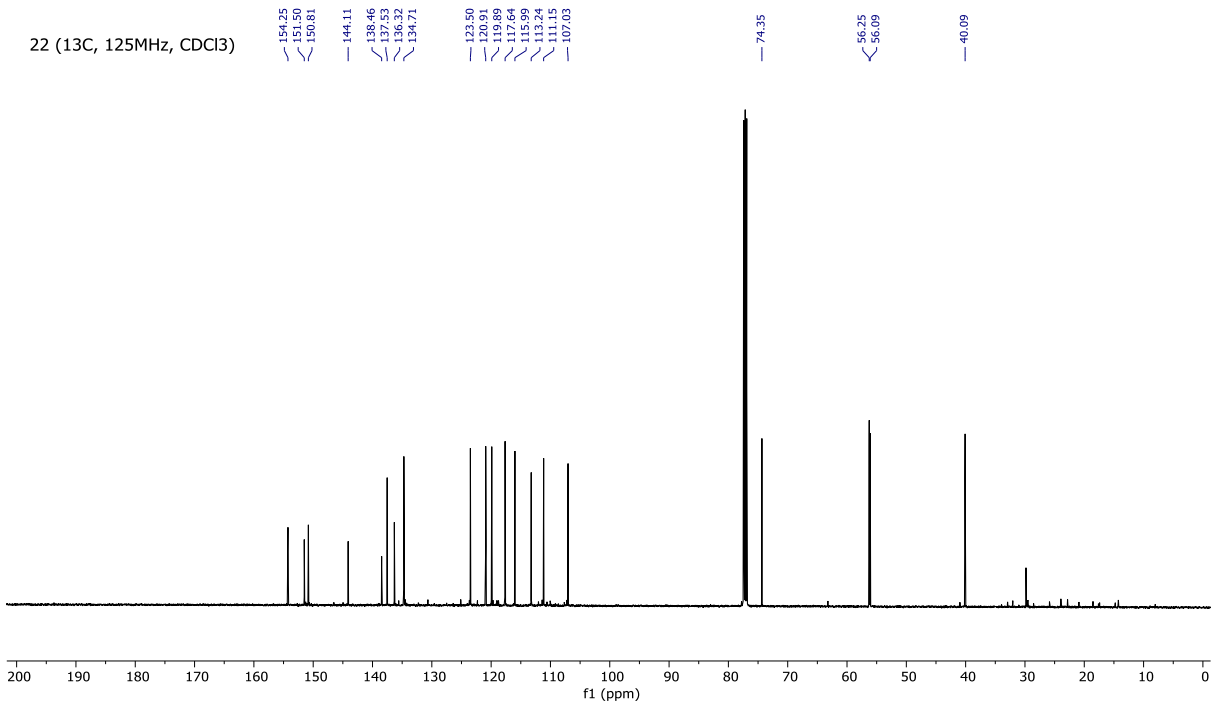
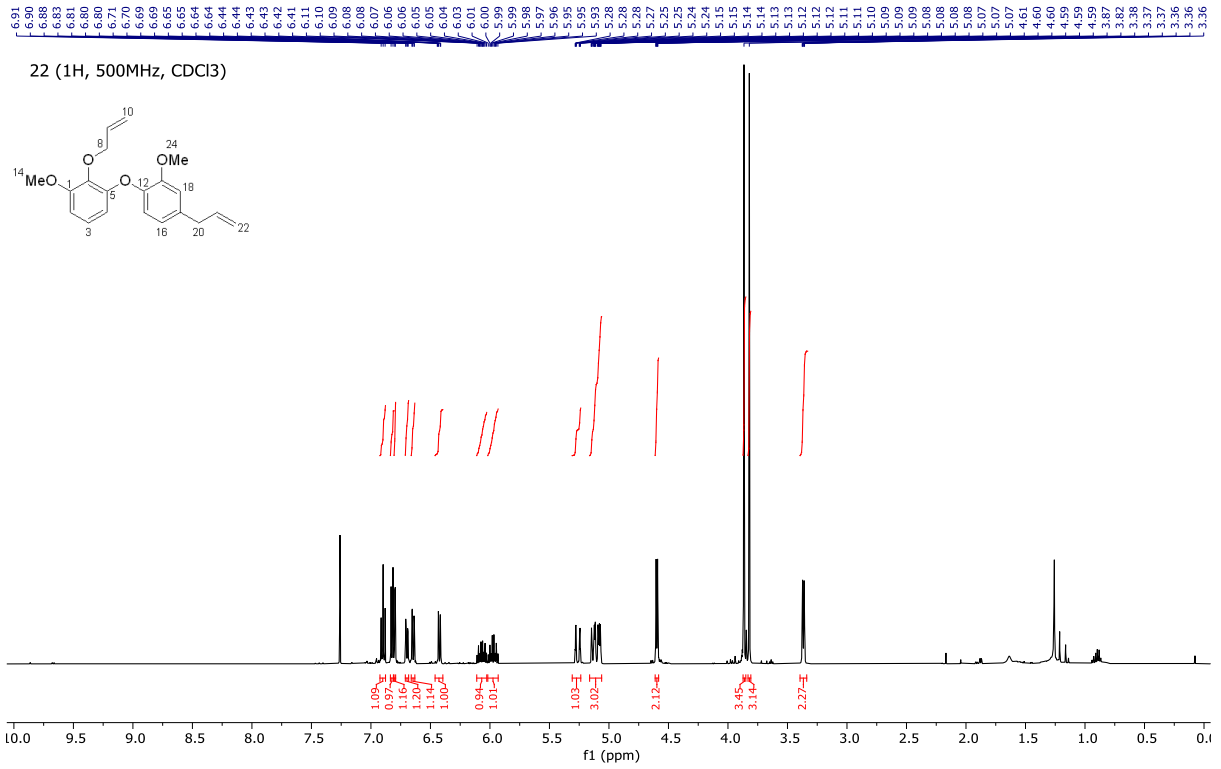


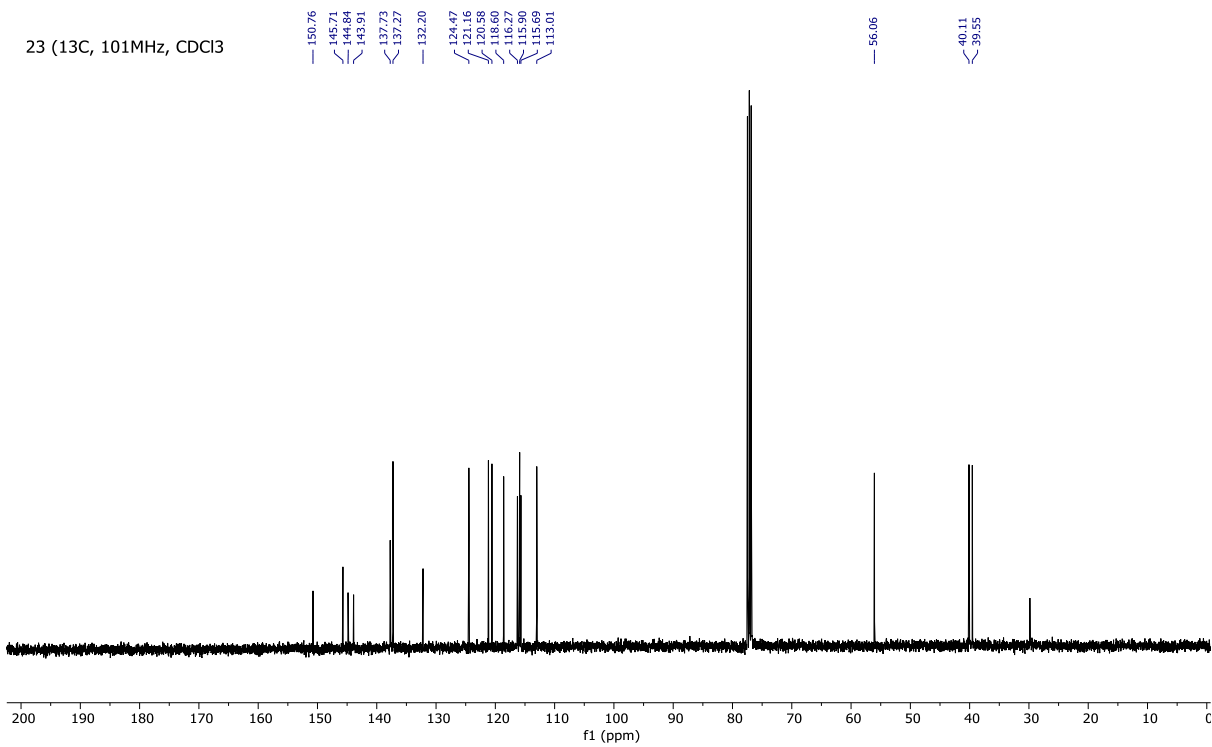
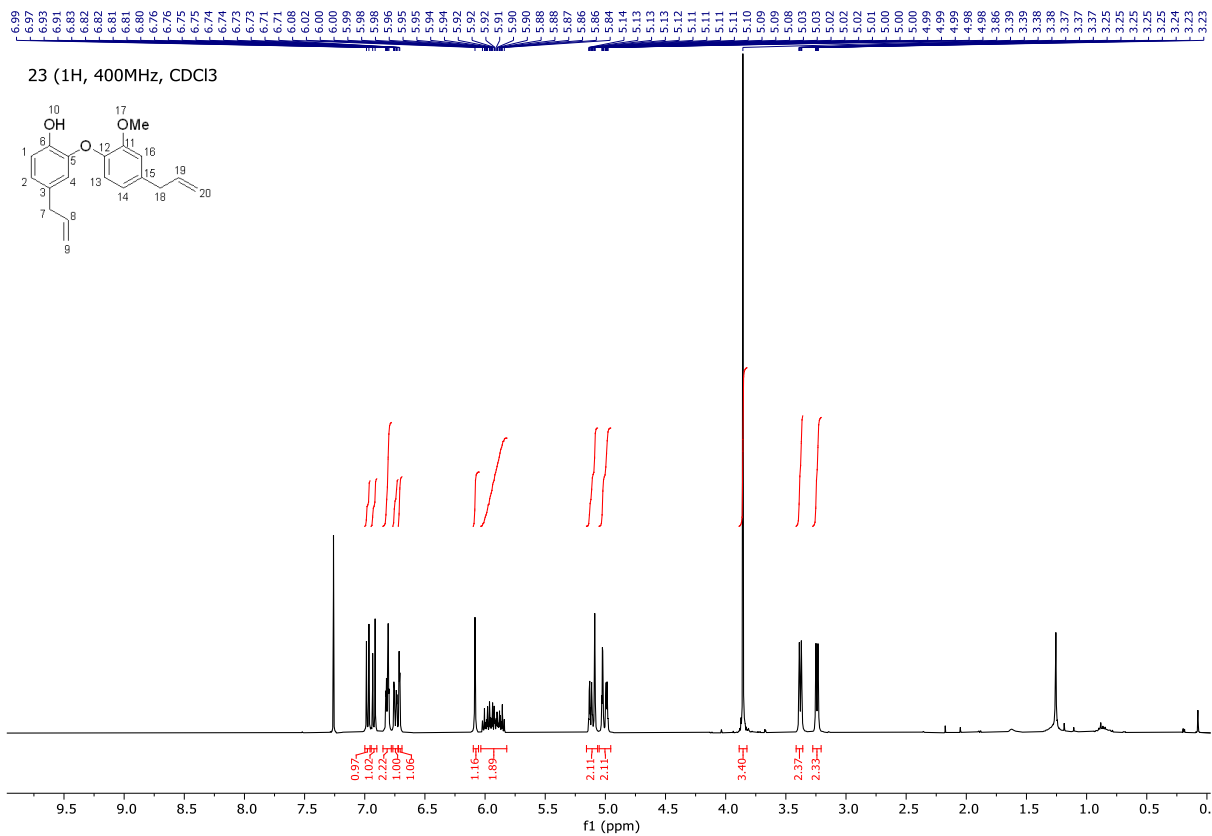


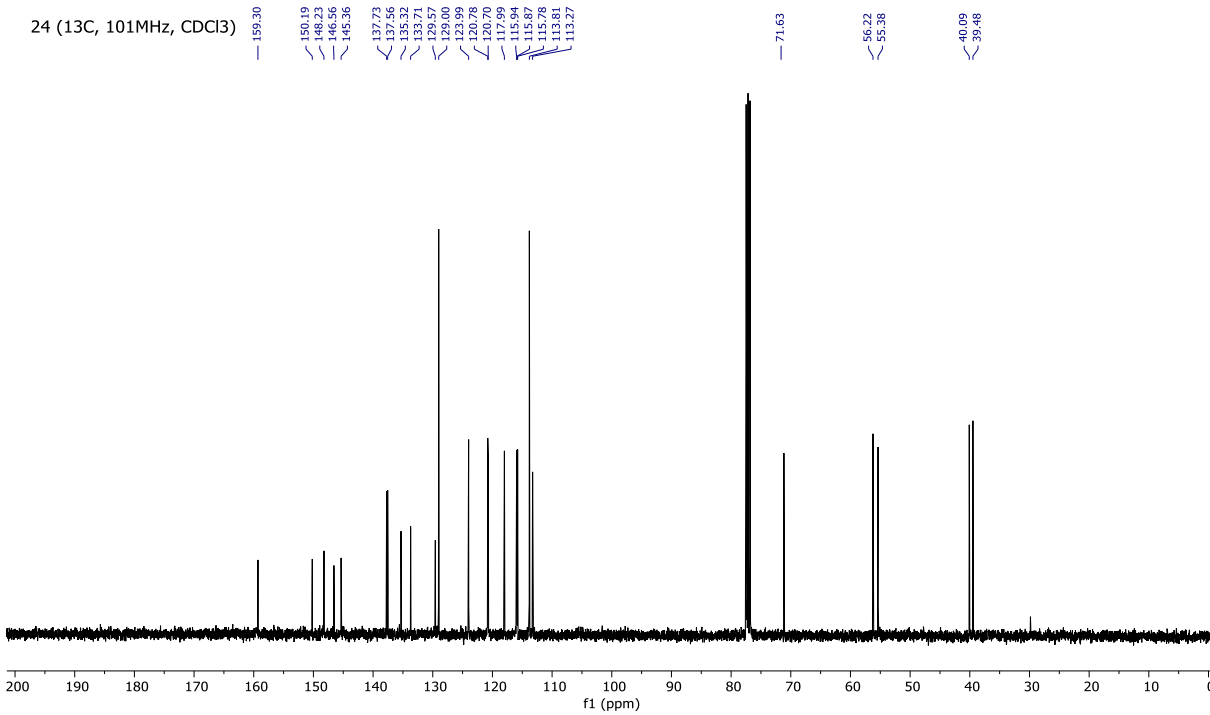
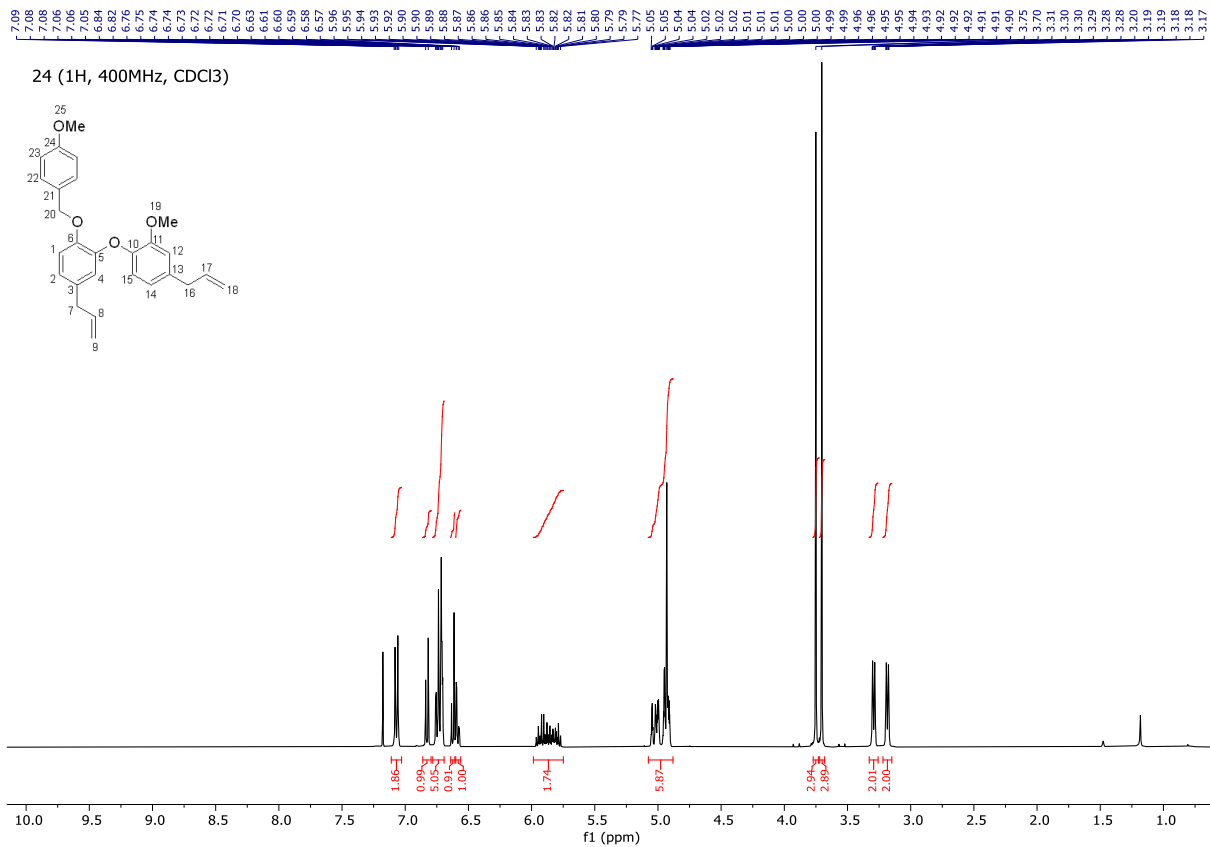




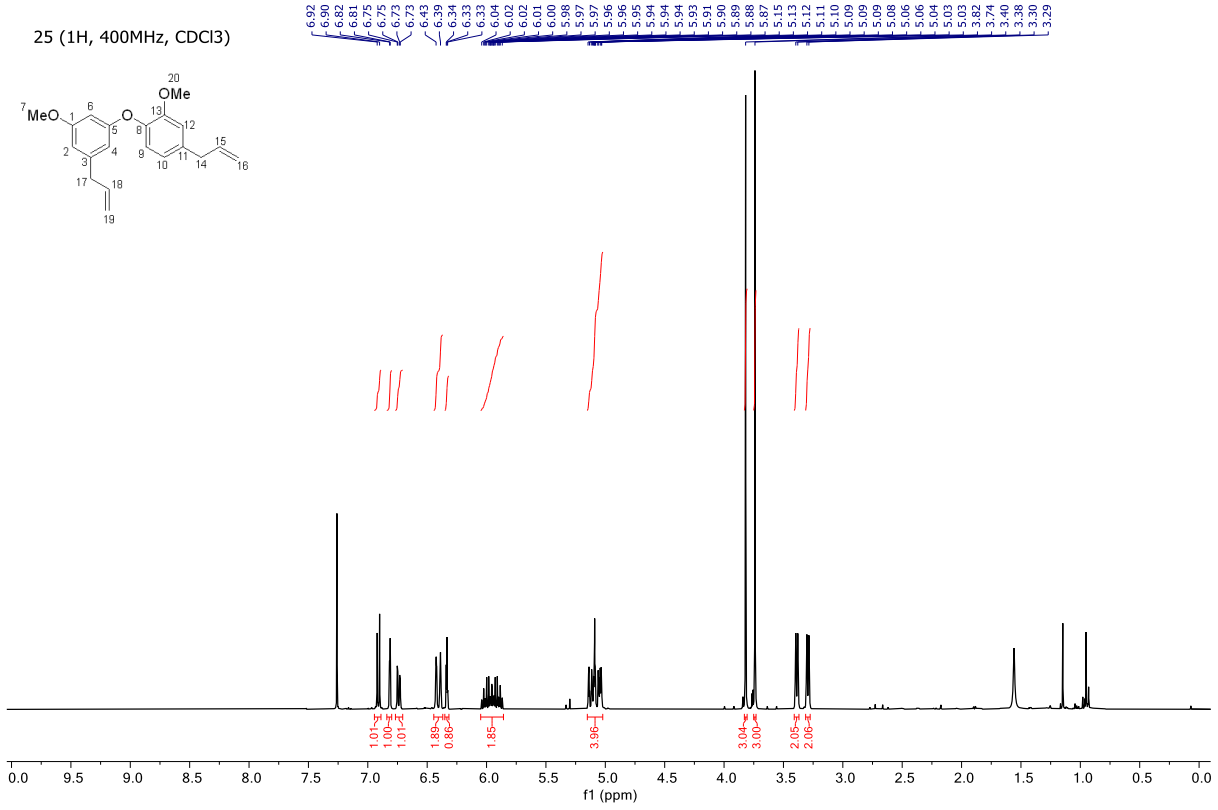
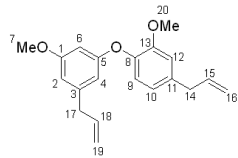




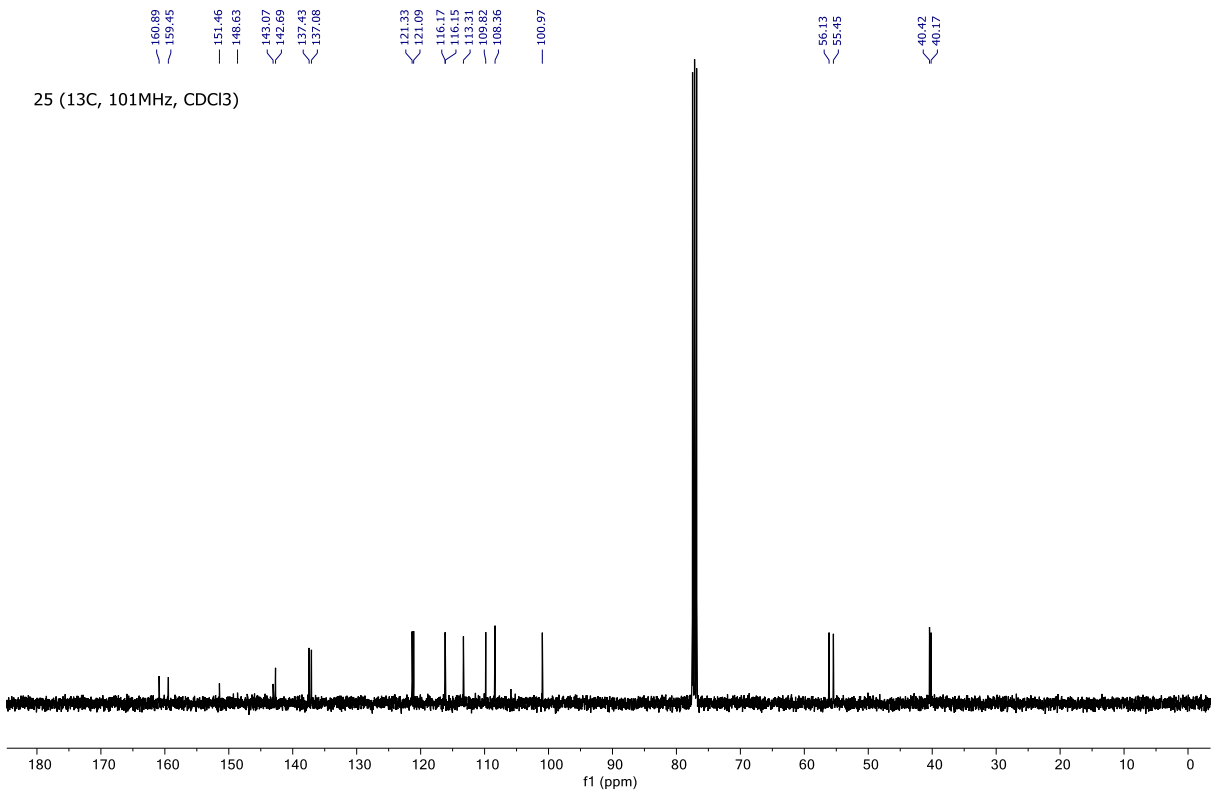


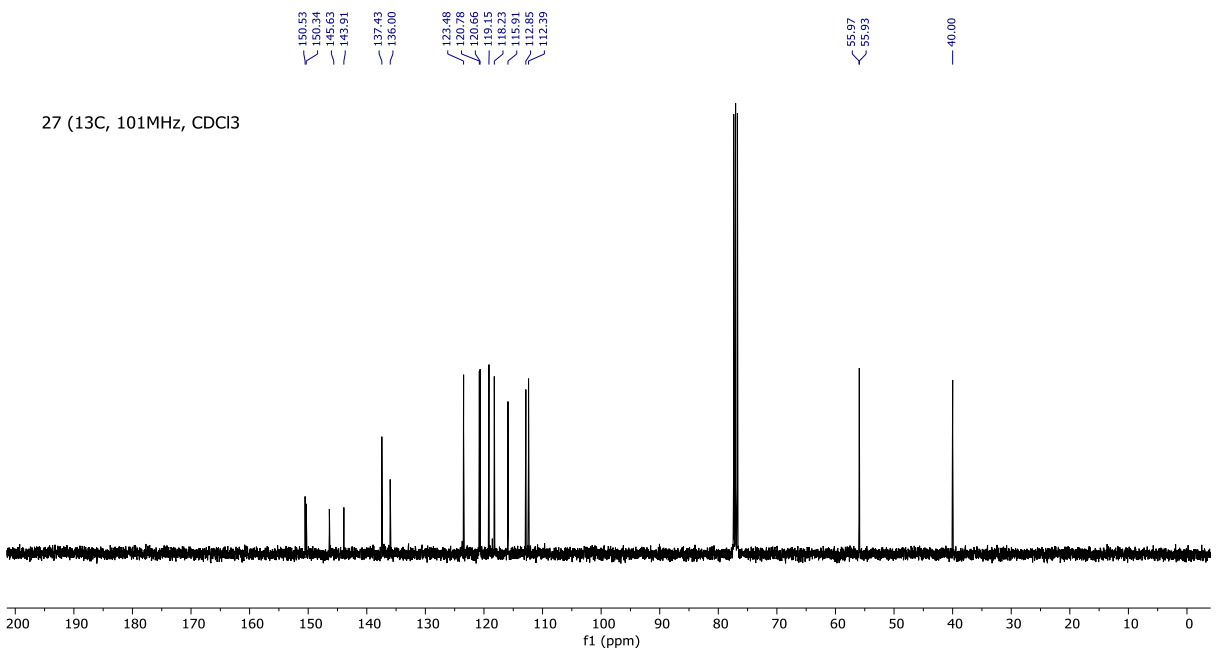
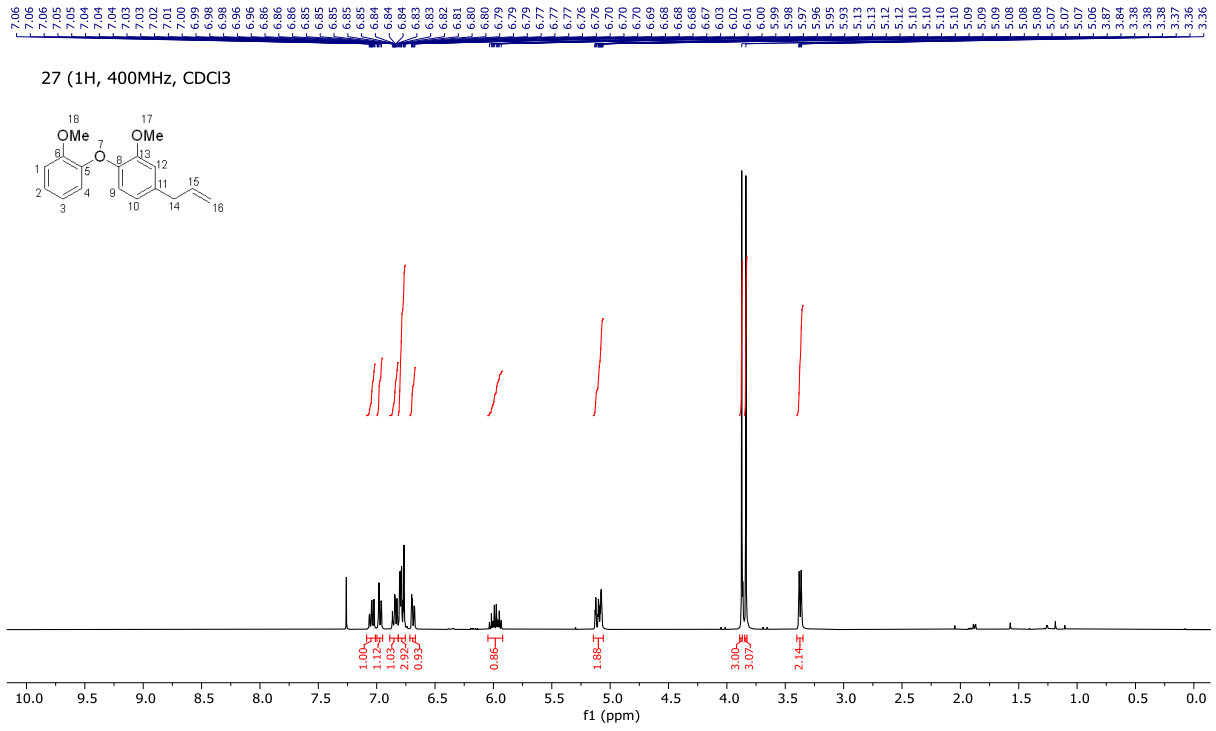


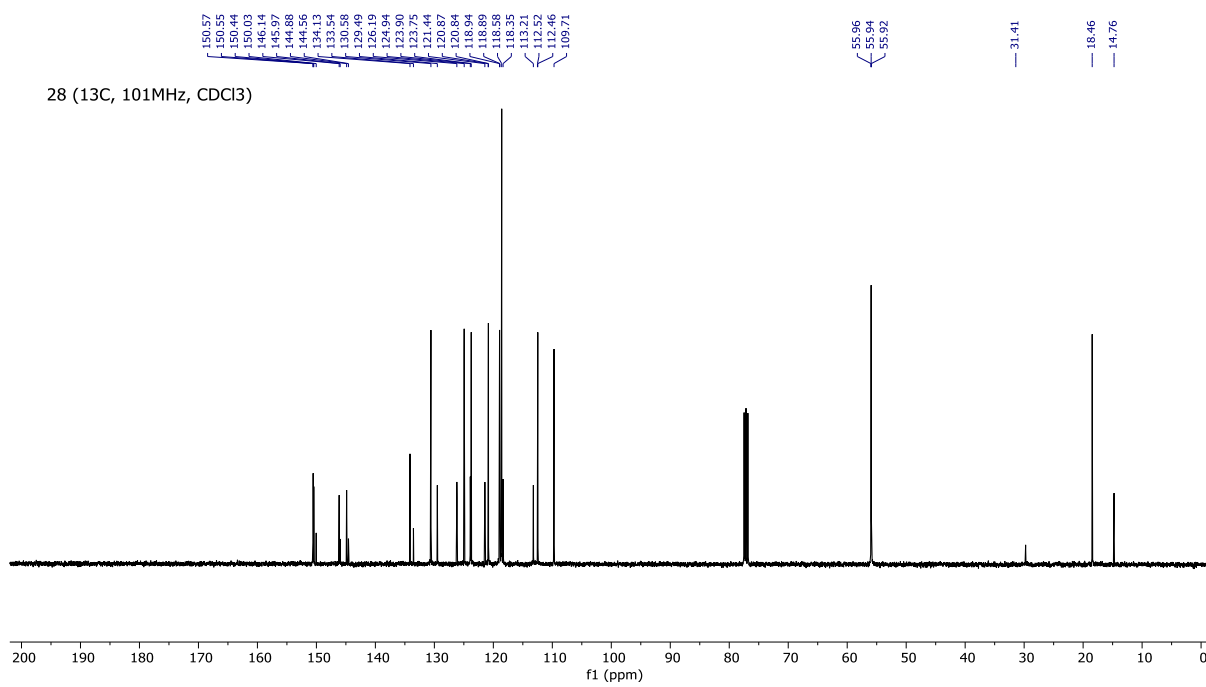
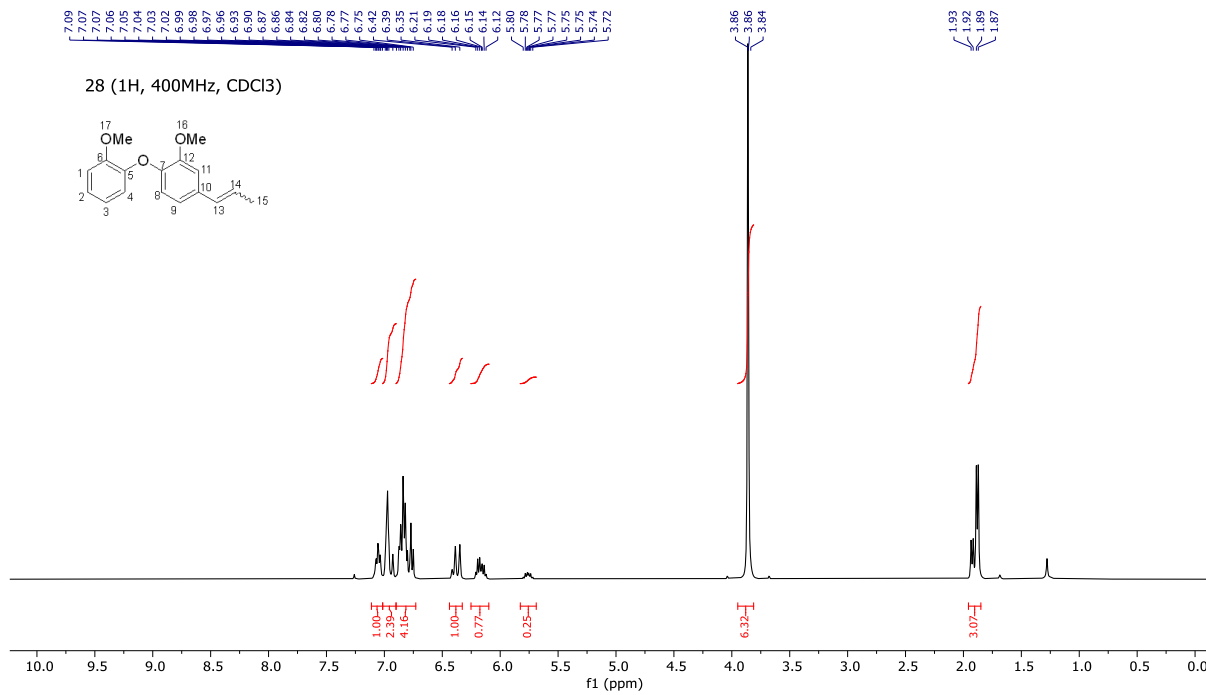
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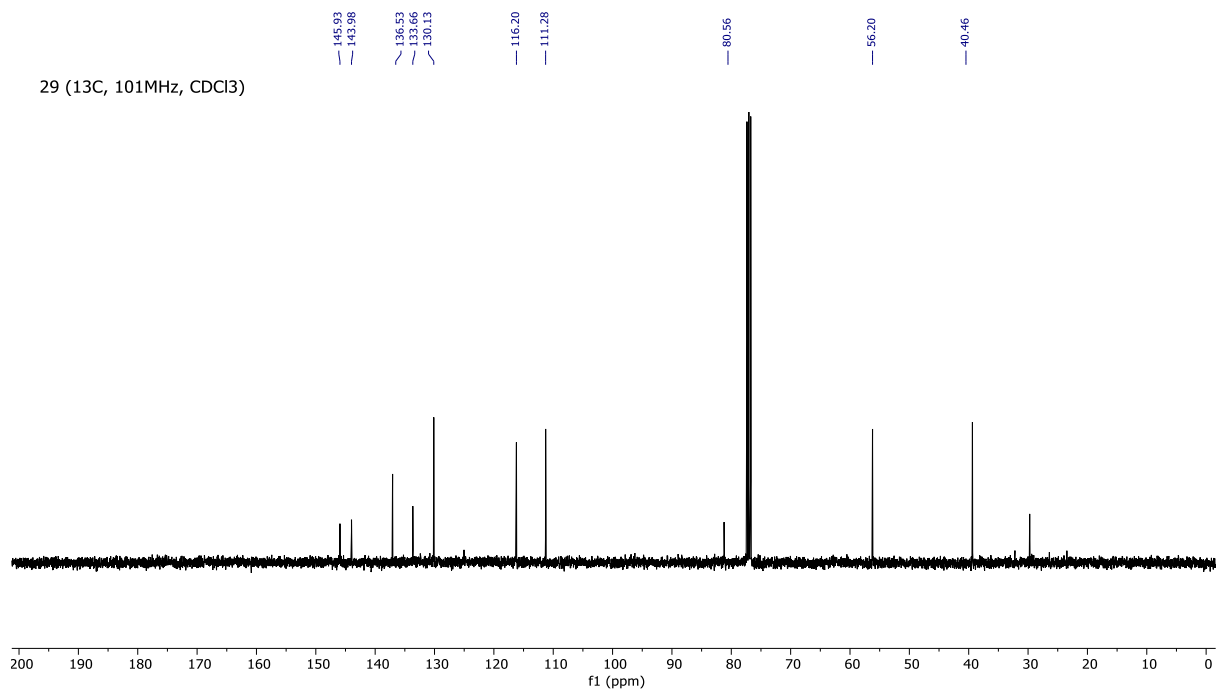
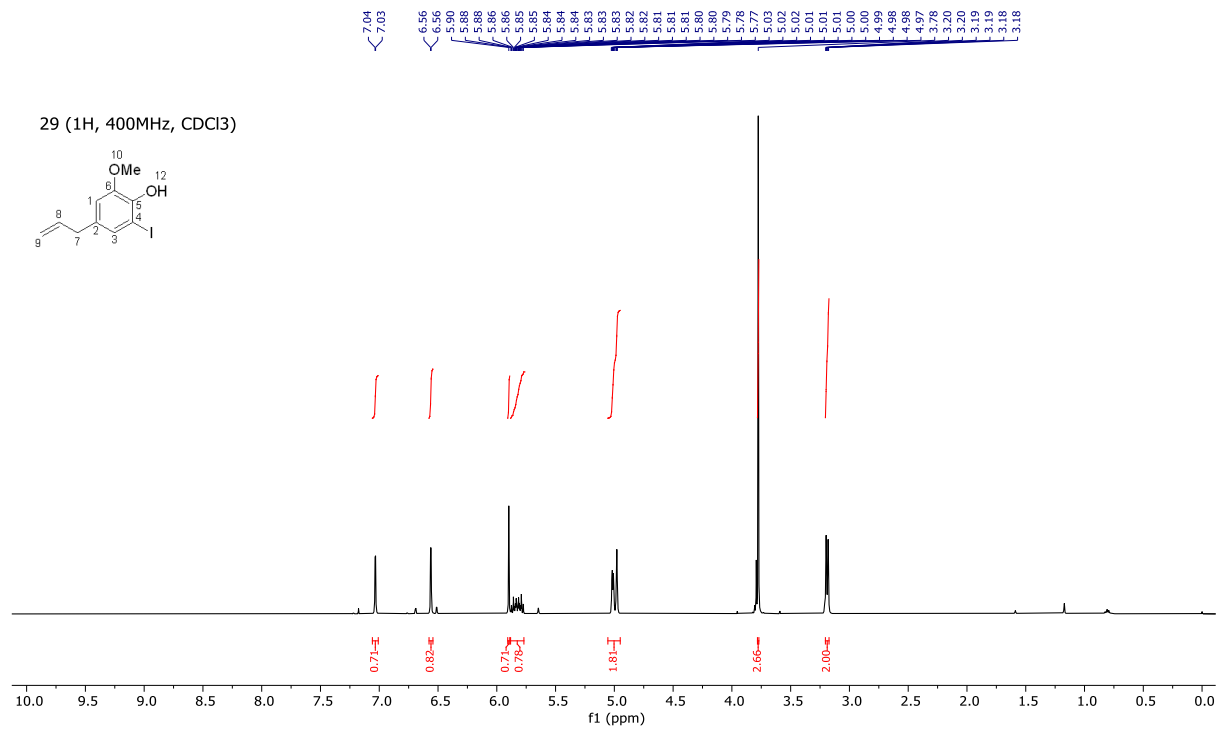


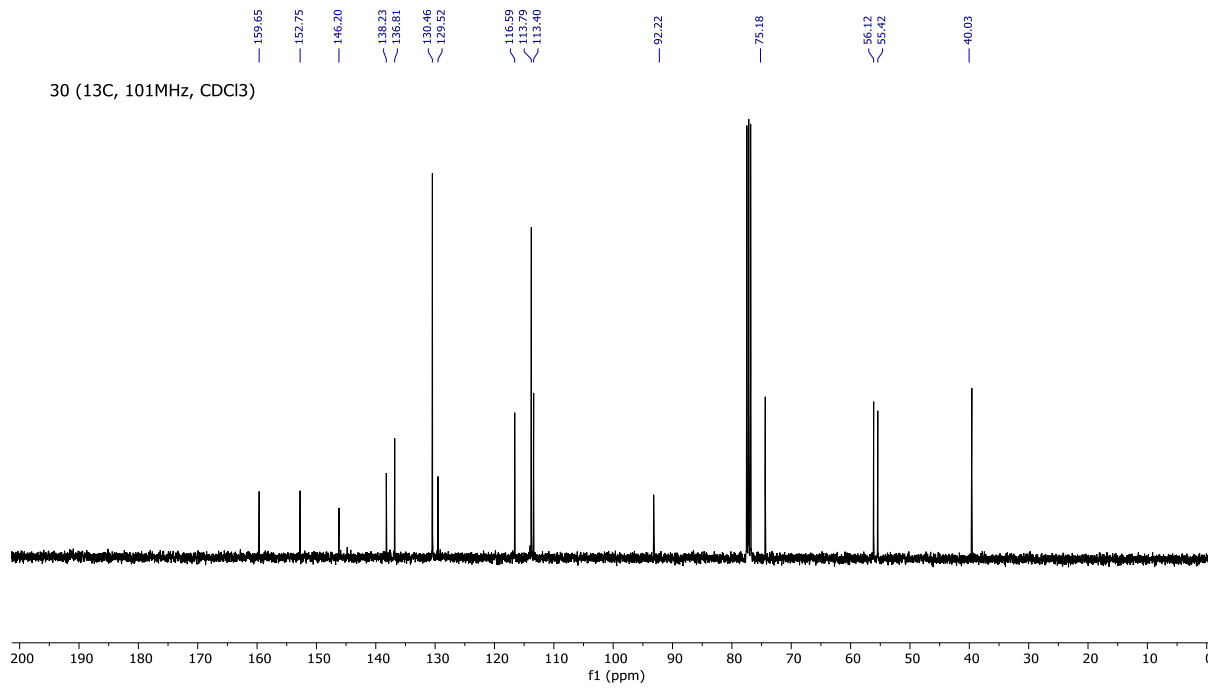
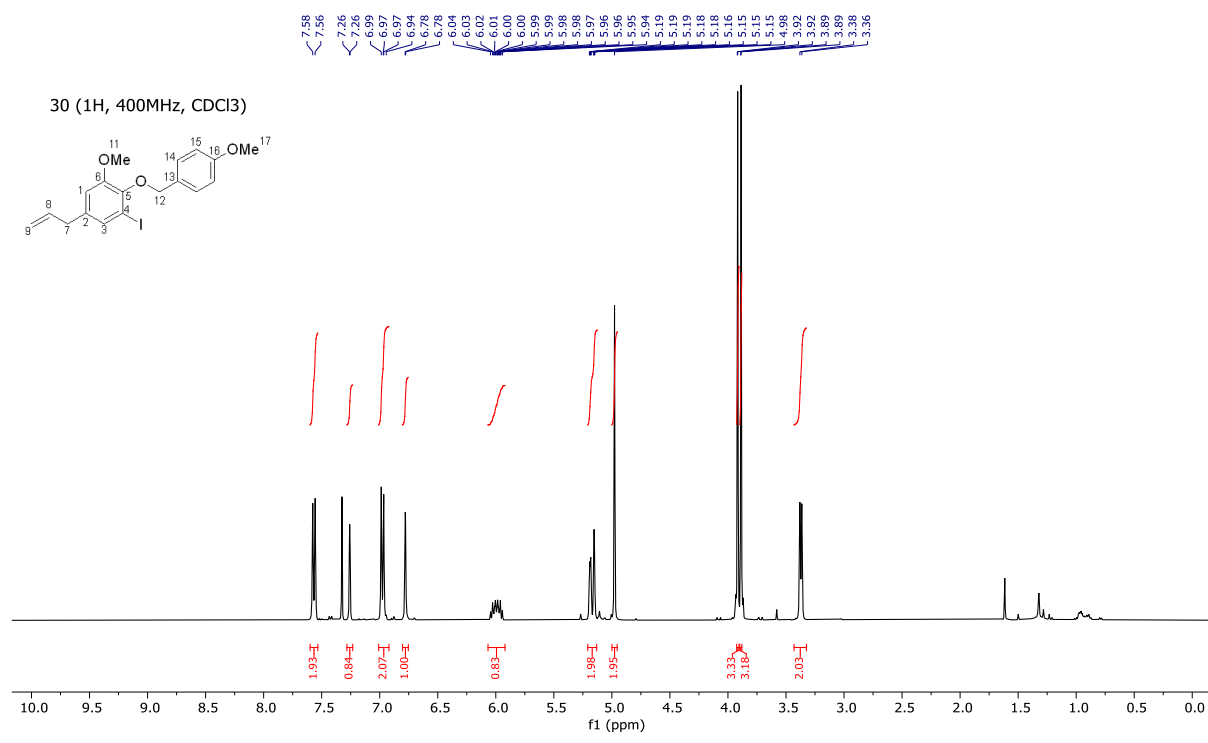
25 (13C, 101MHz, CDCl3)





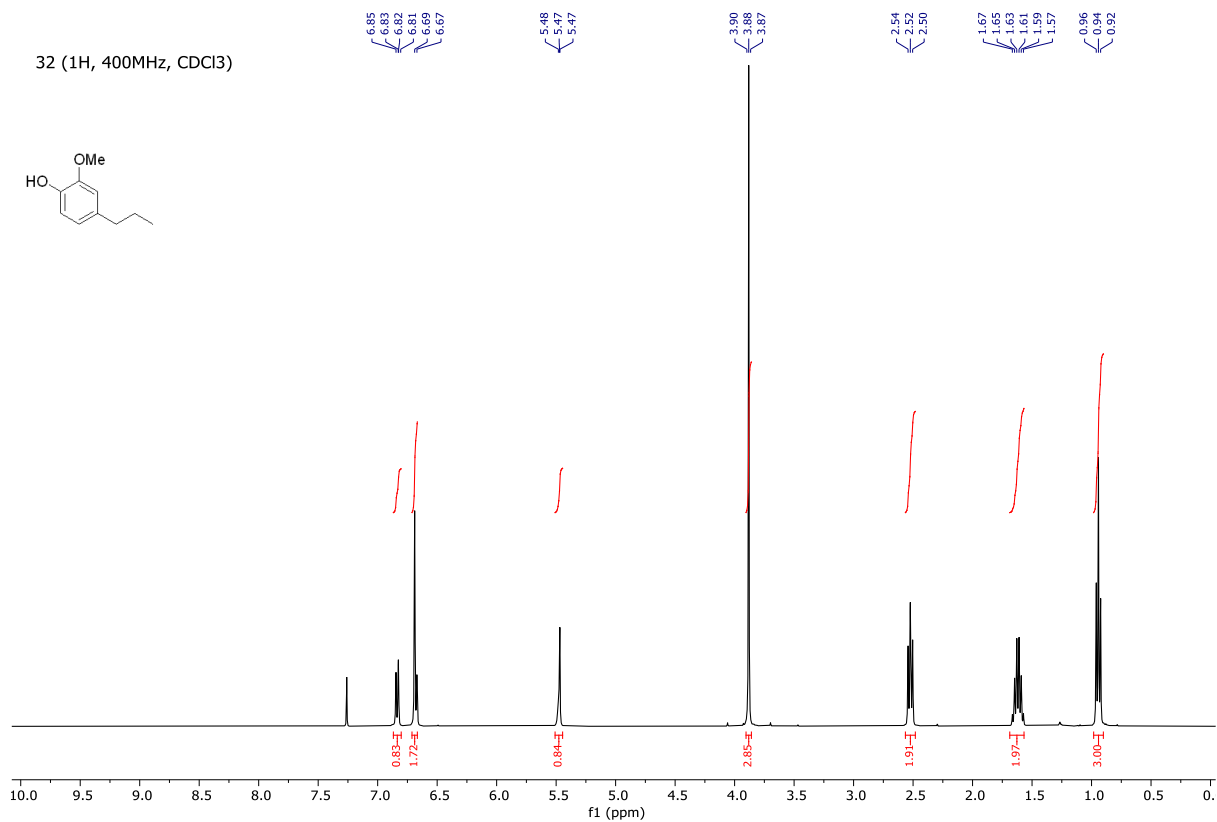
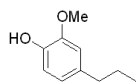




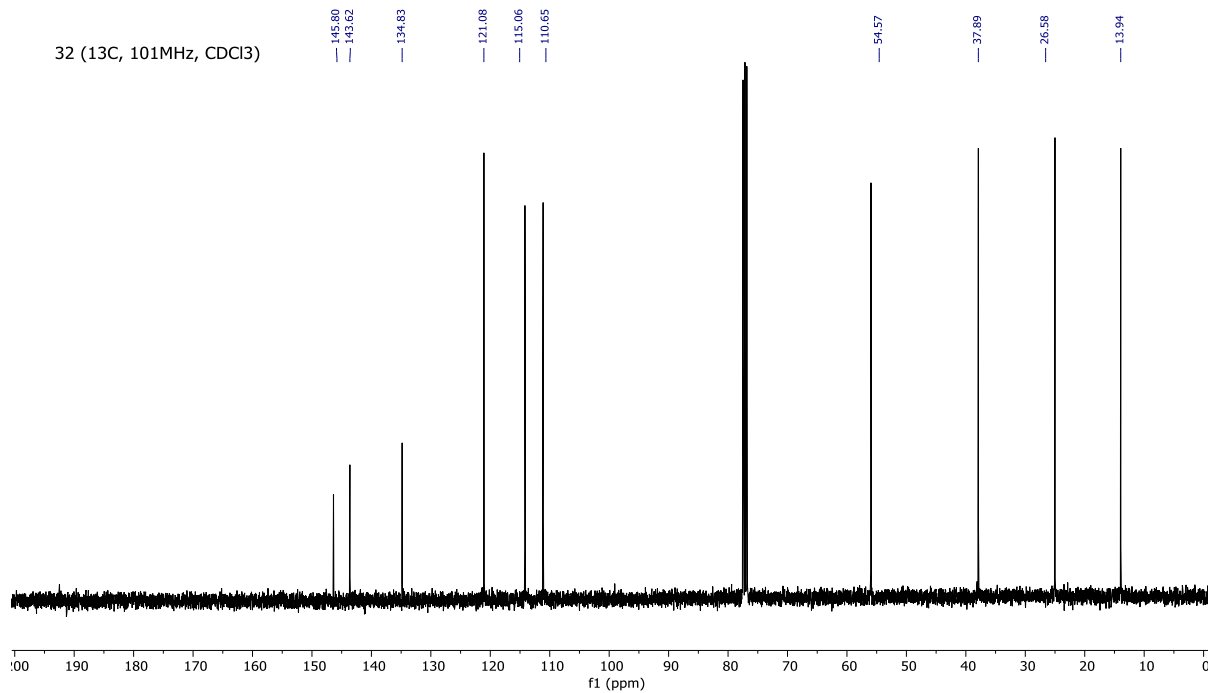


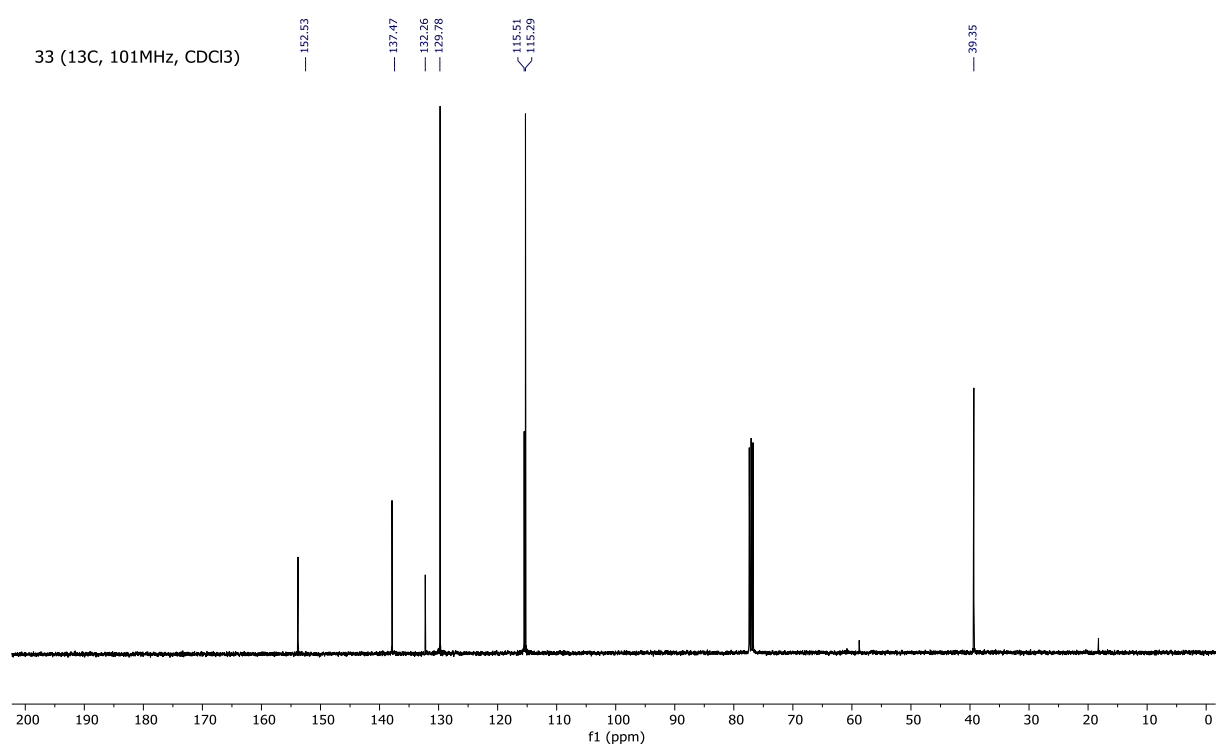
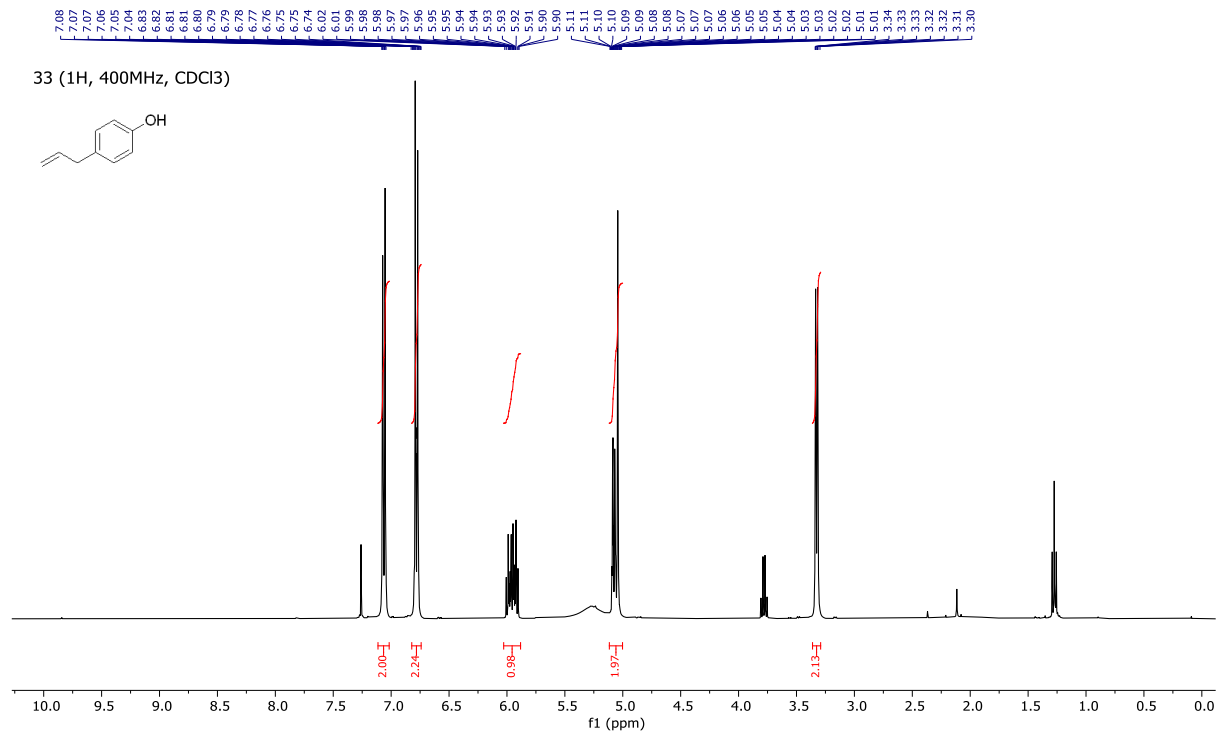


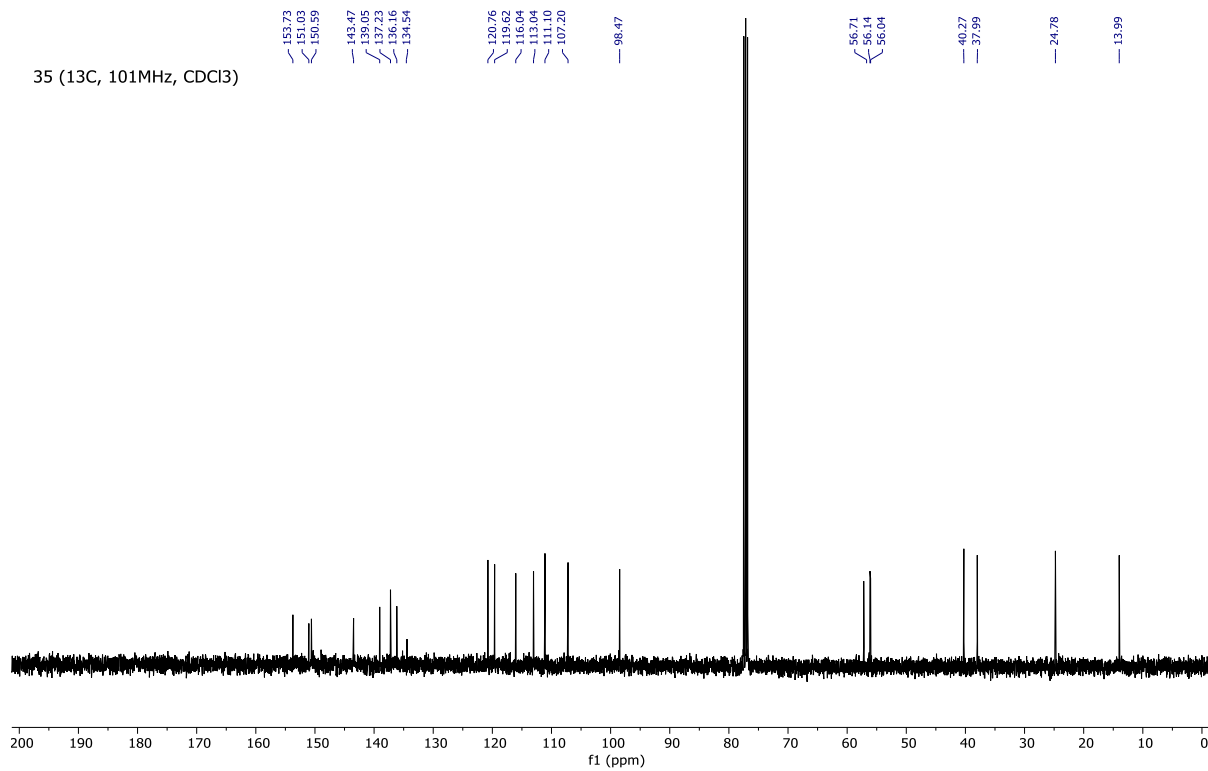
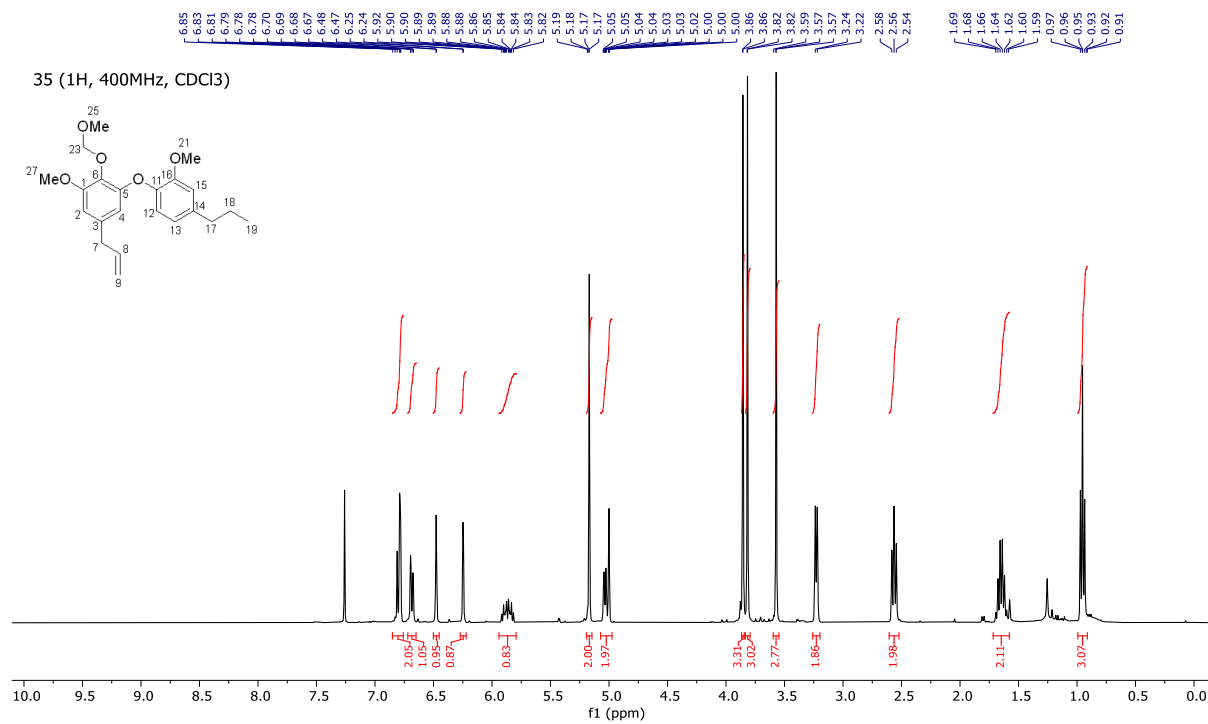
32 (1H, 400MHz, CDCl3)

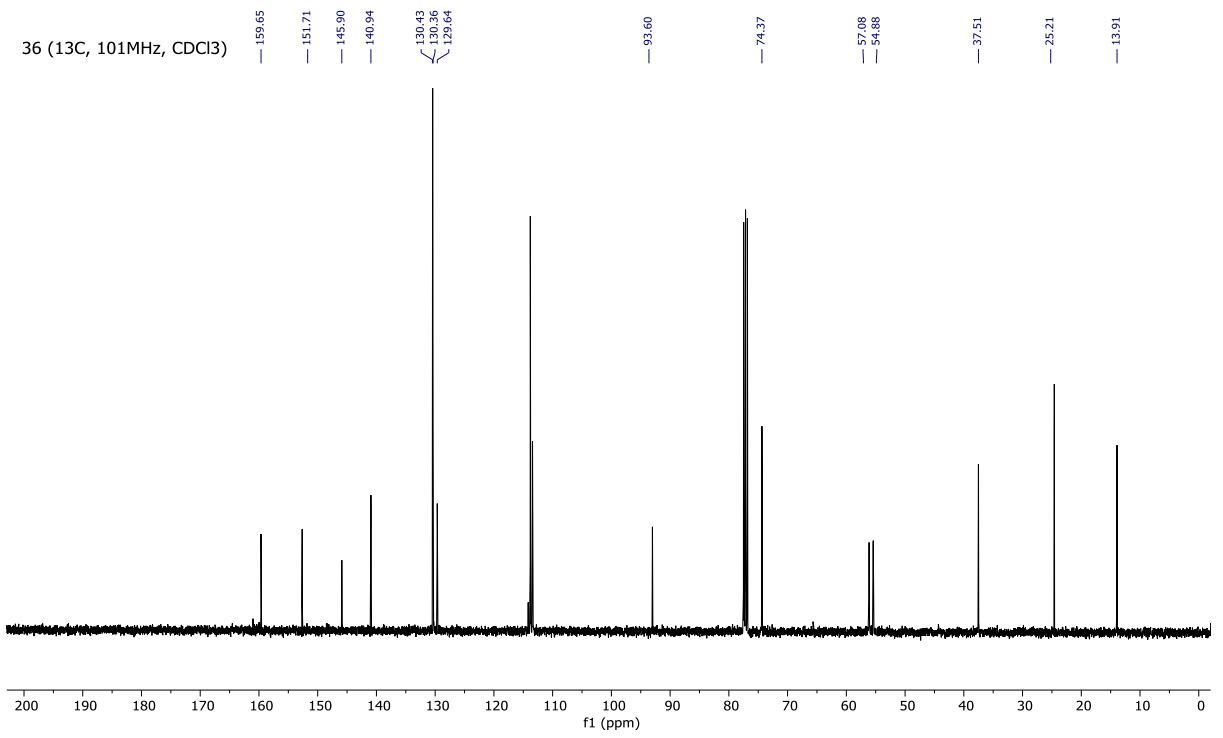
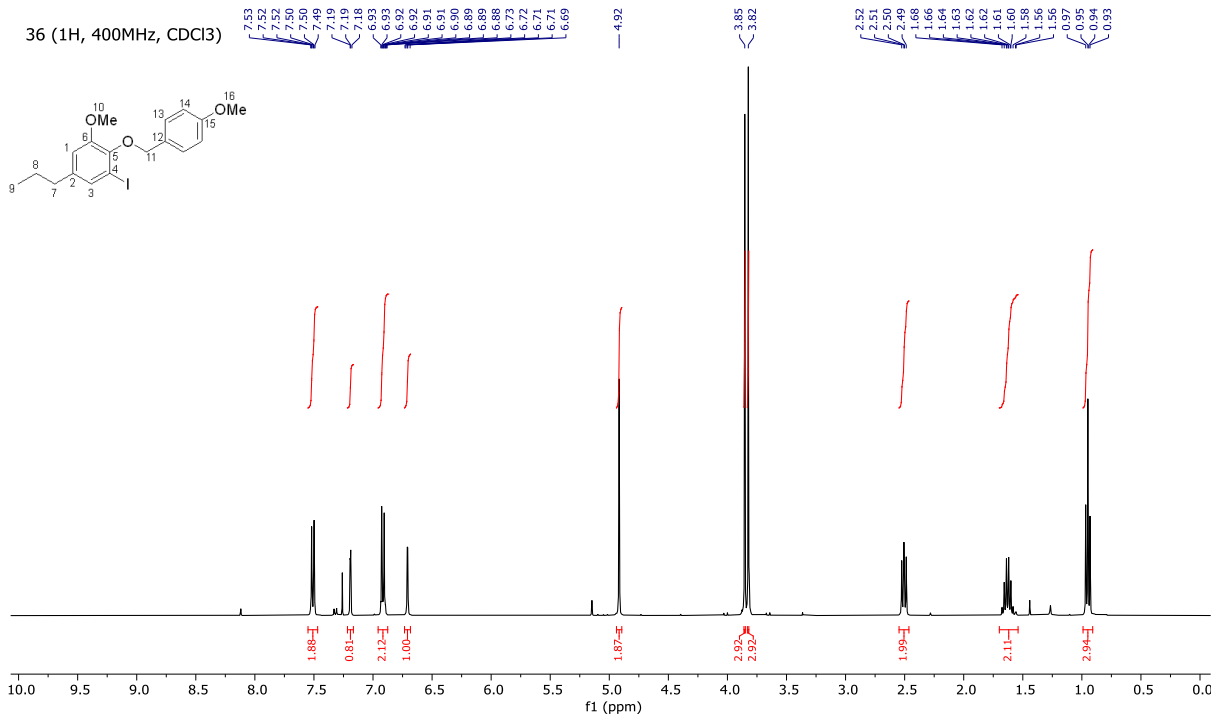


32 (13C, 101MHz, CDCl3)

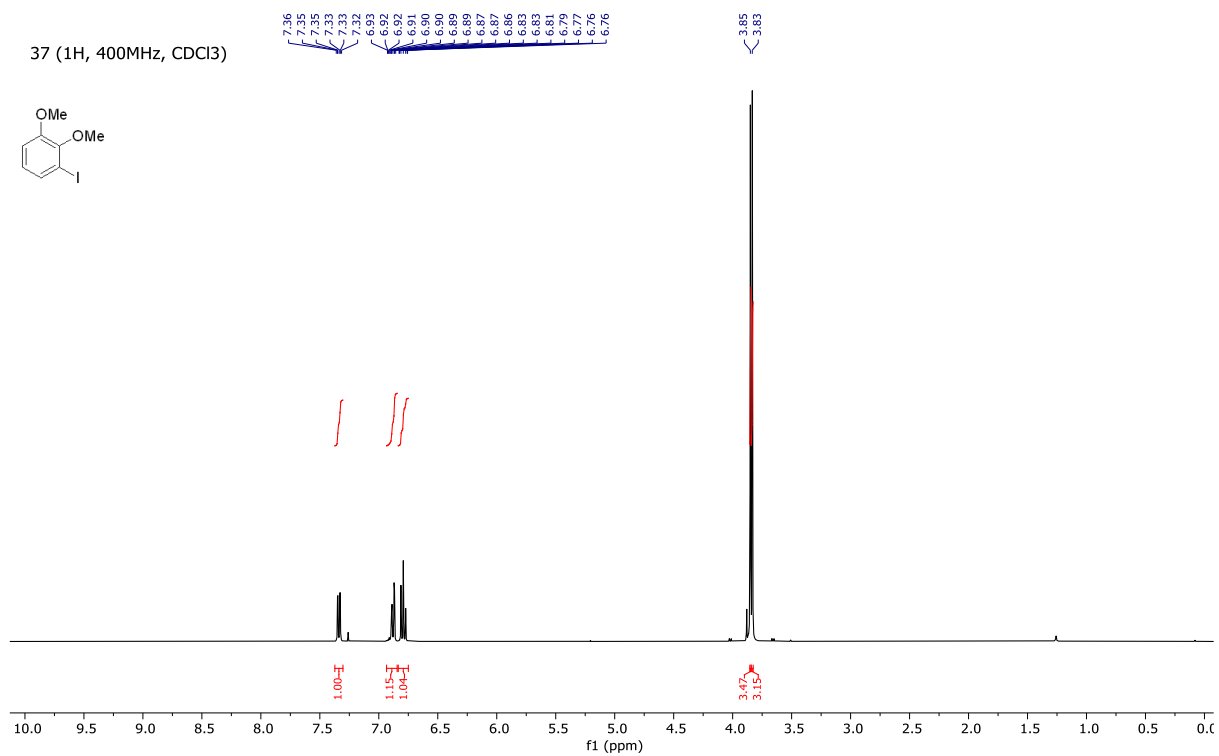




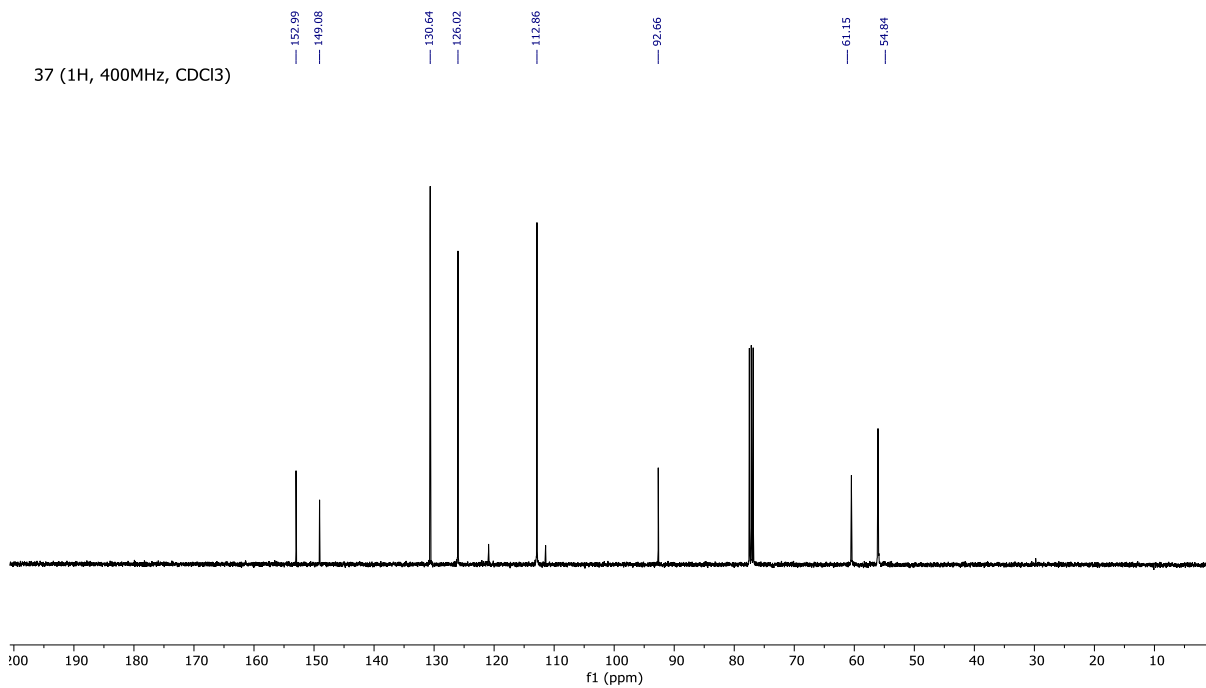


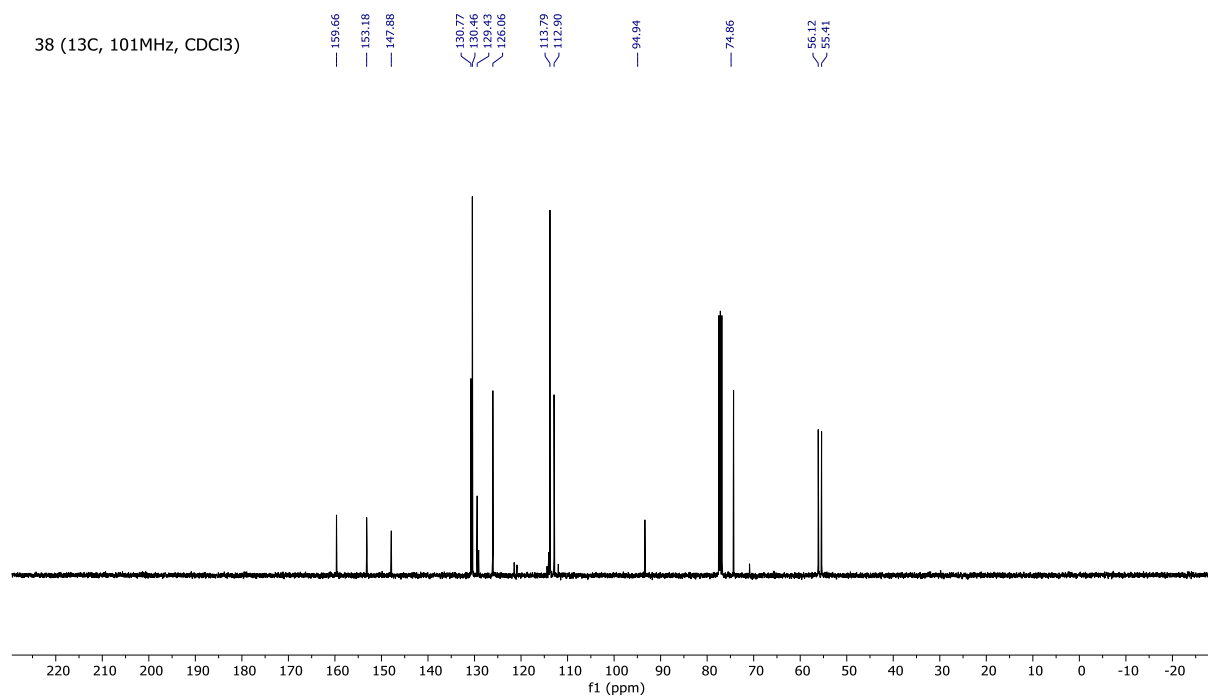
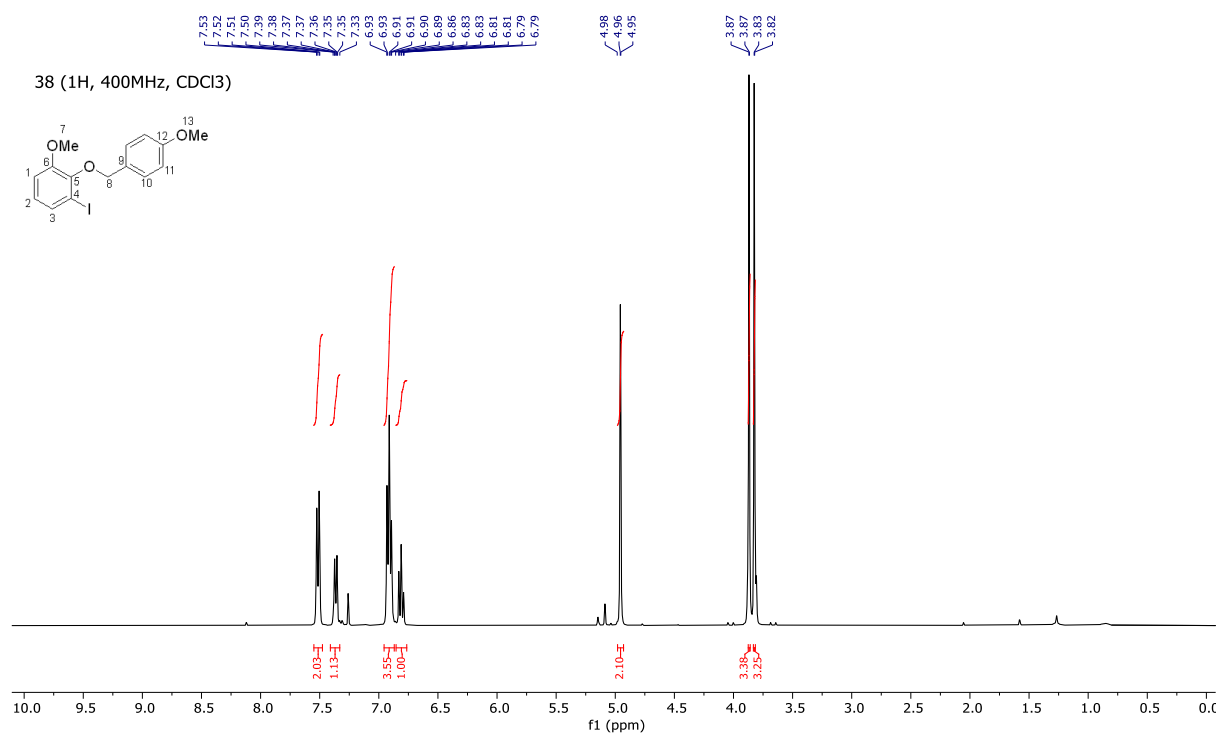


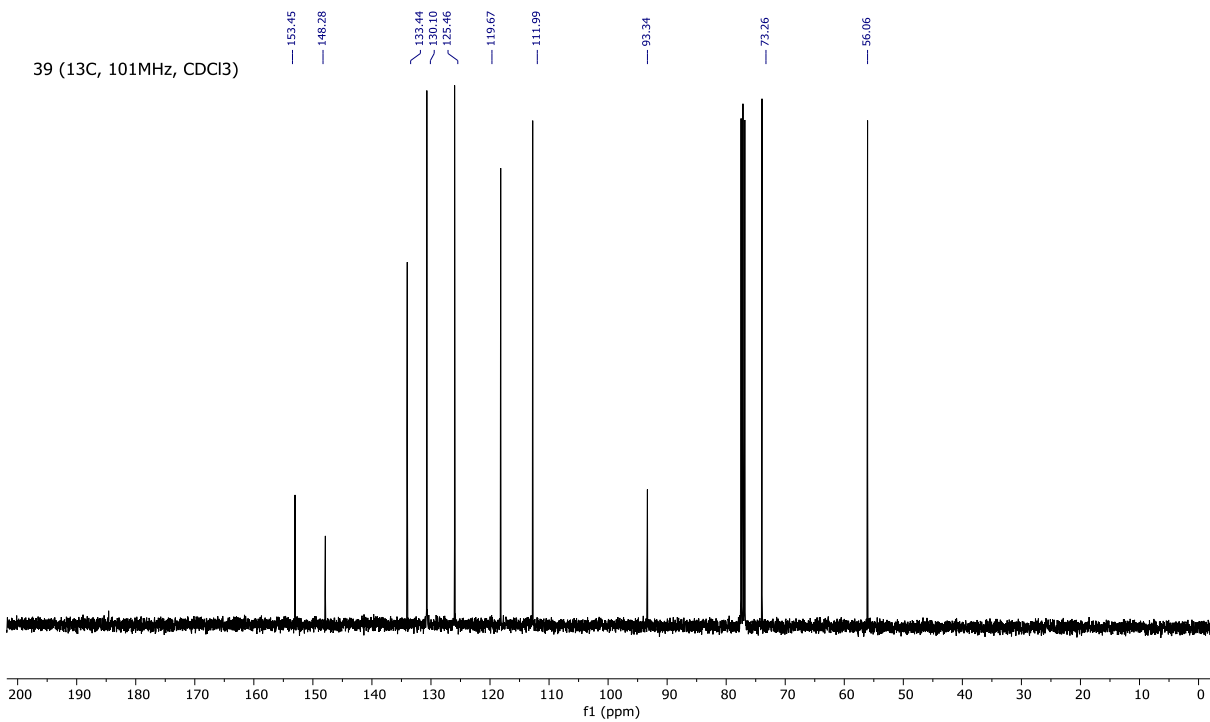
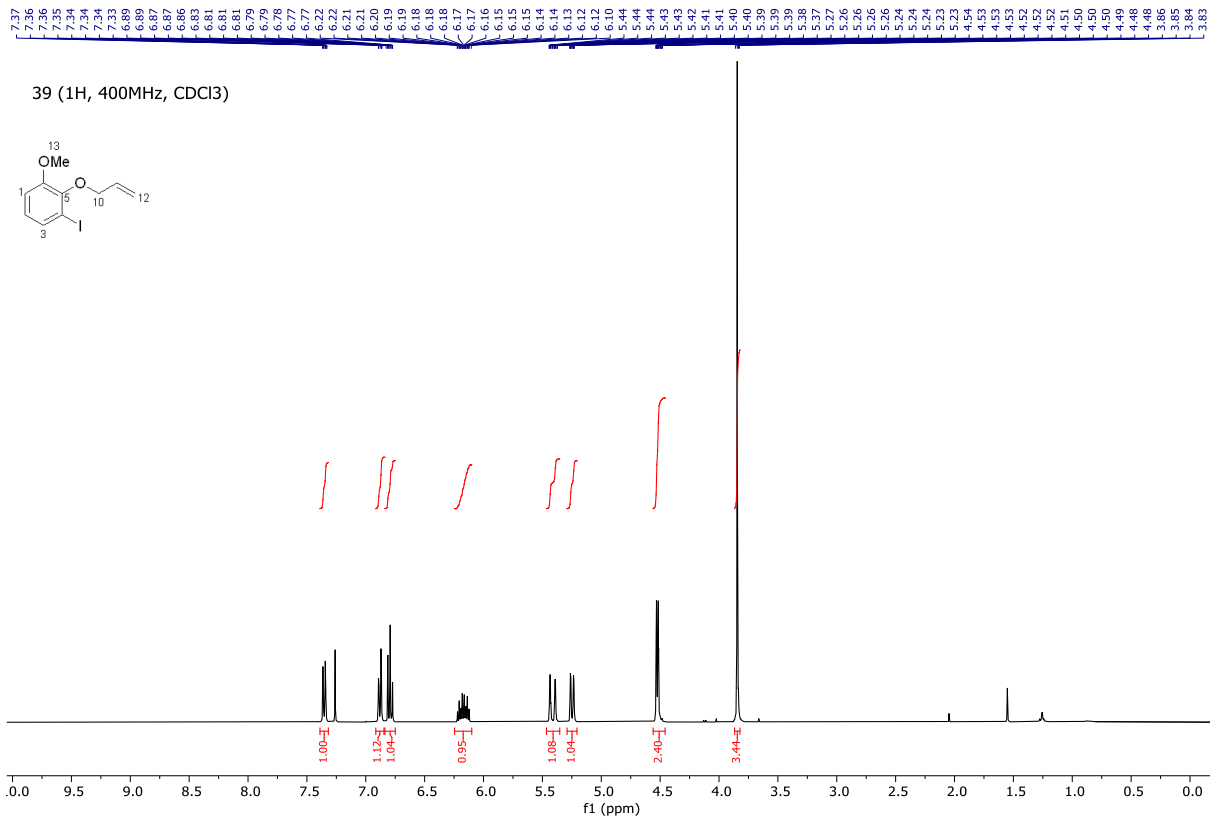
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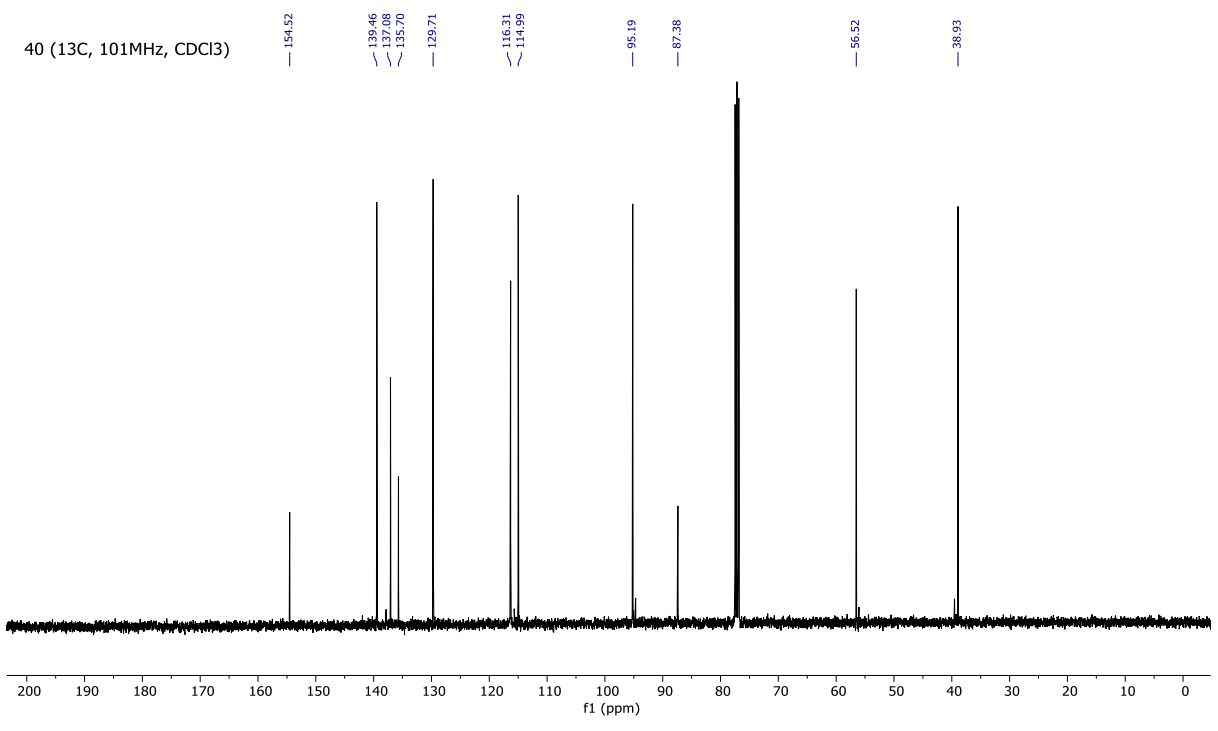
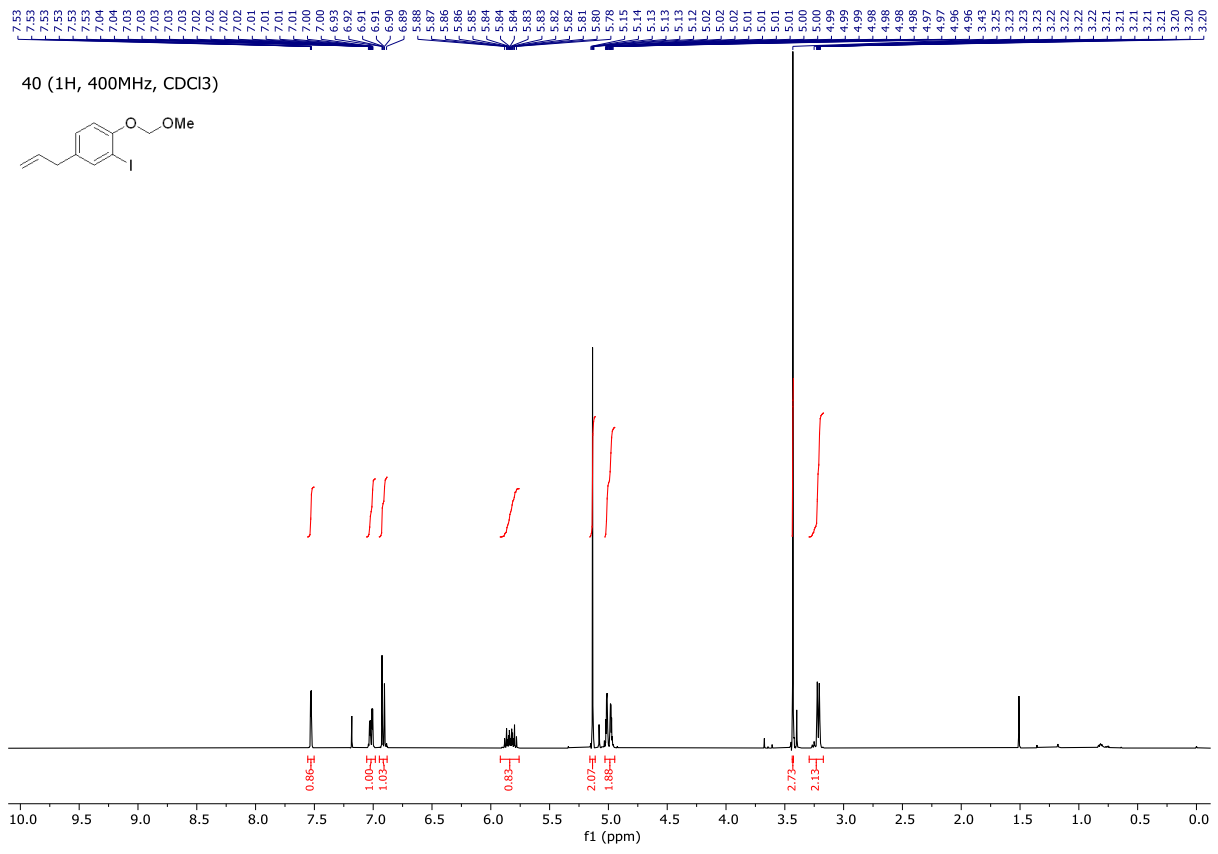


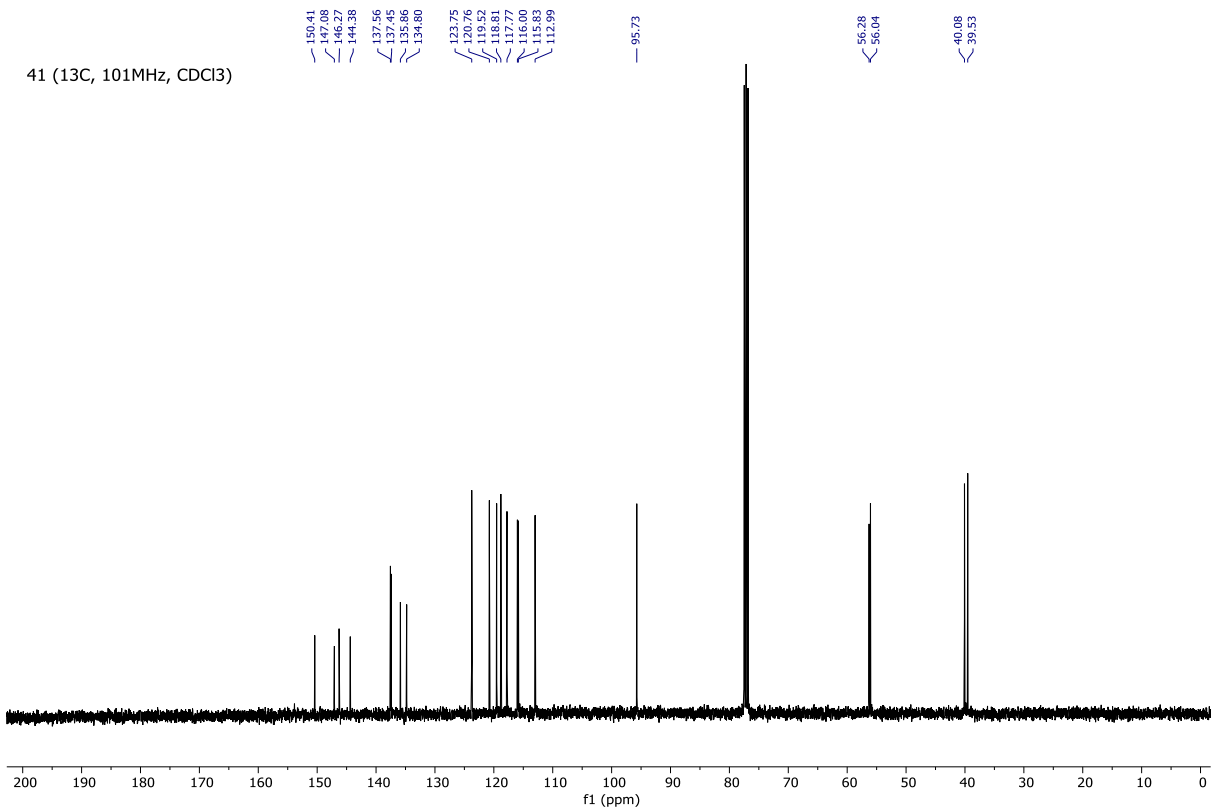
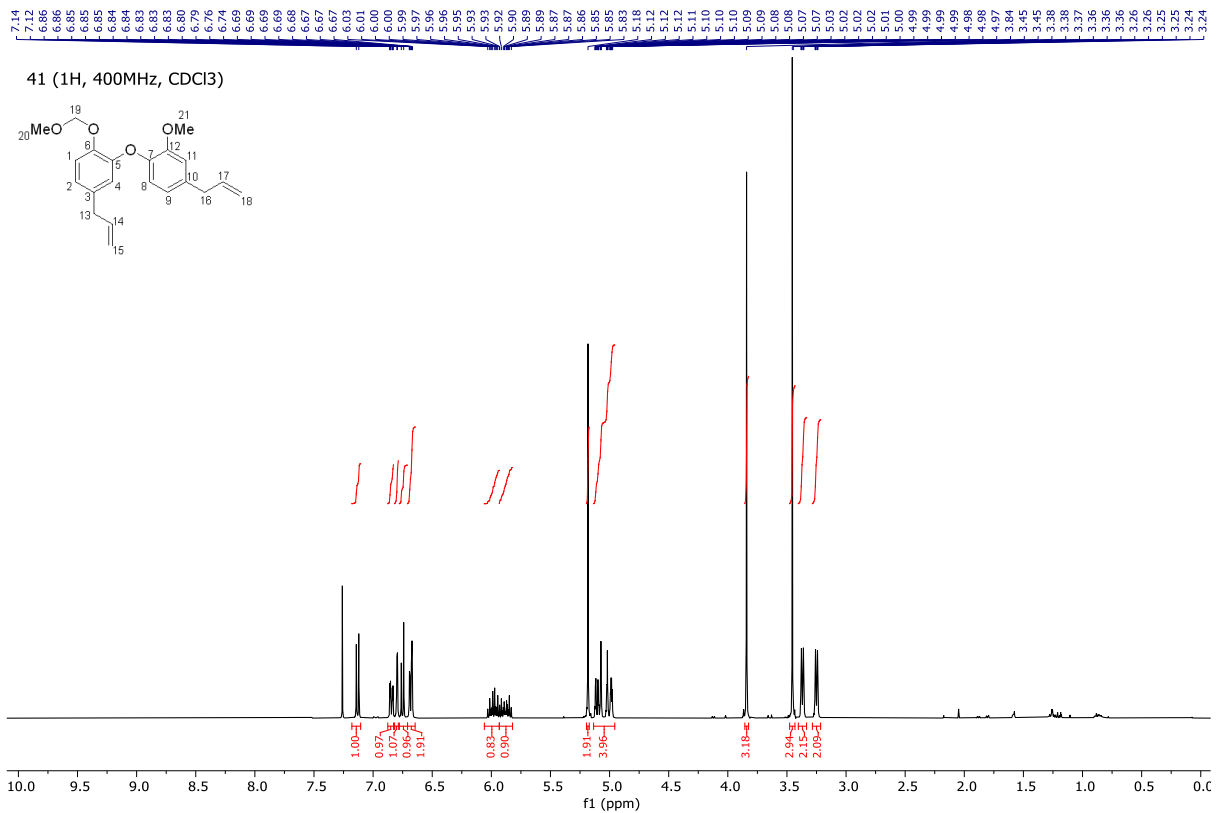
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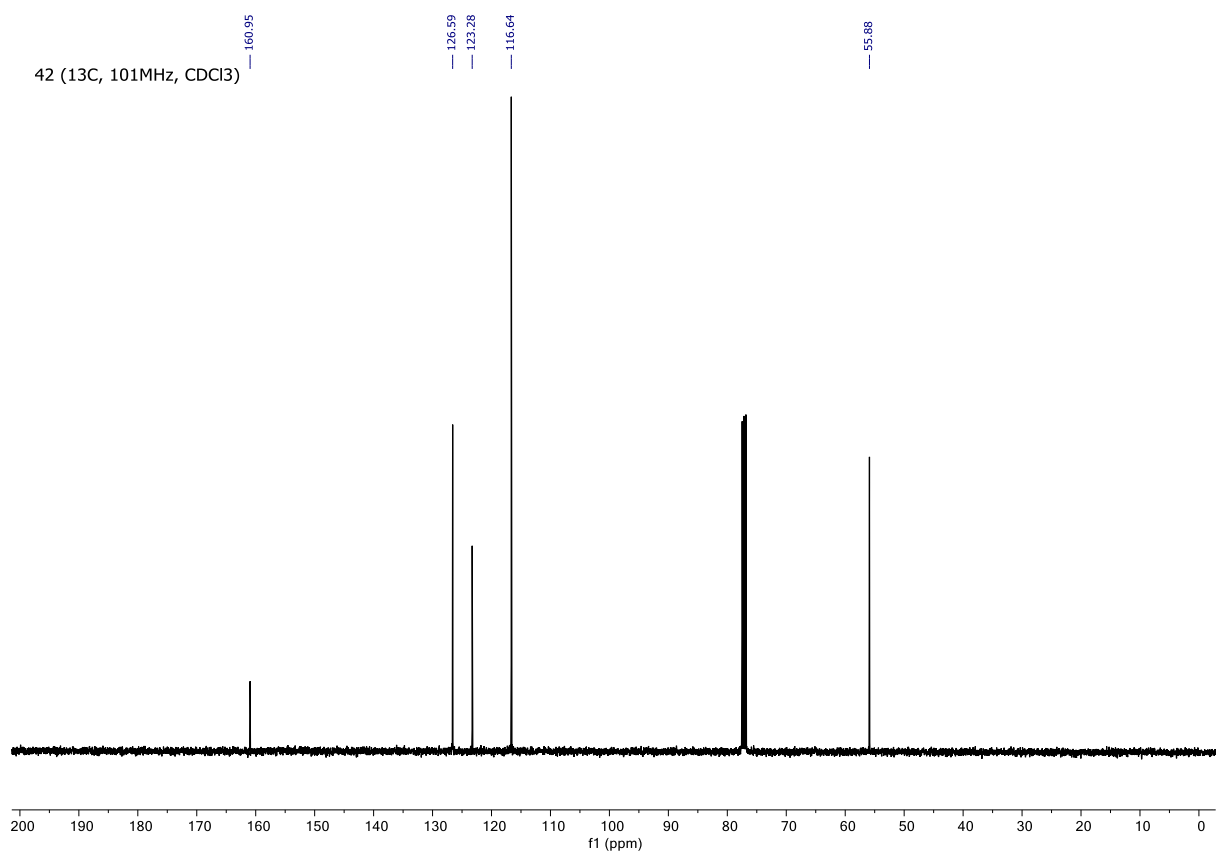
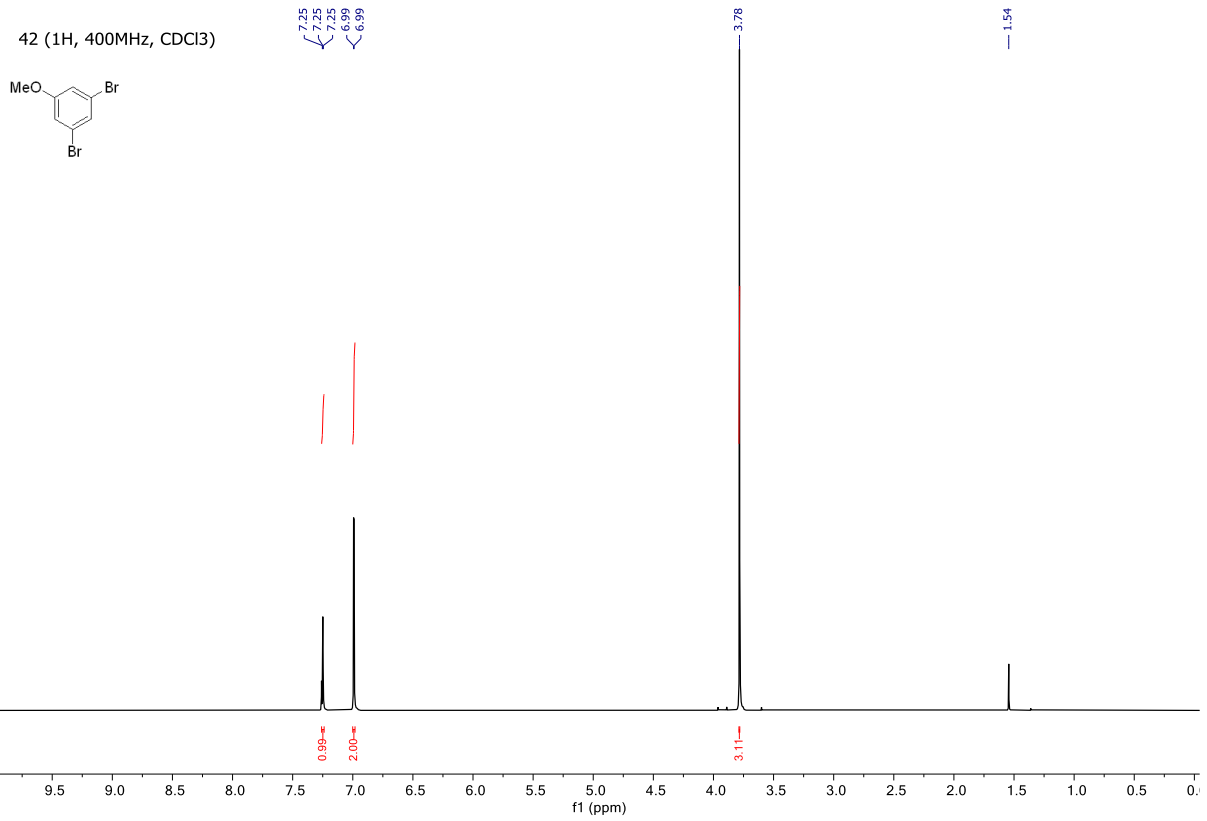


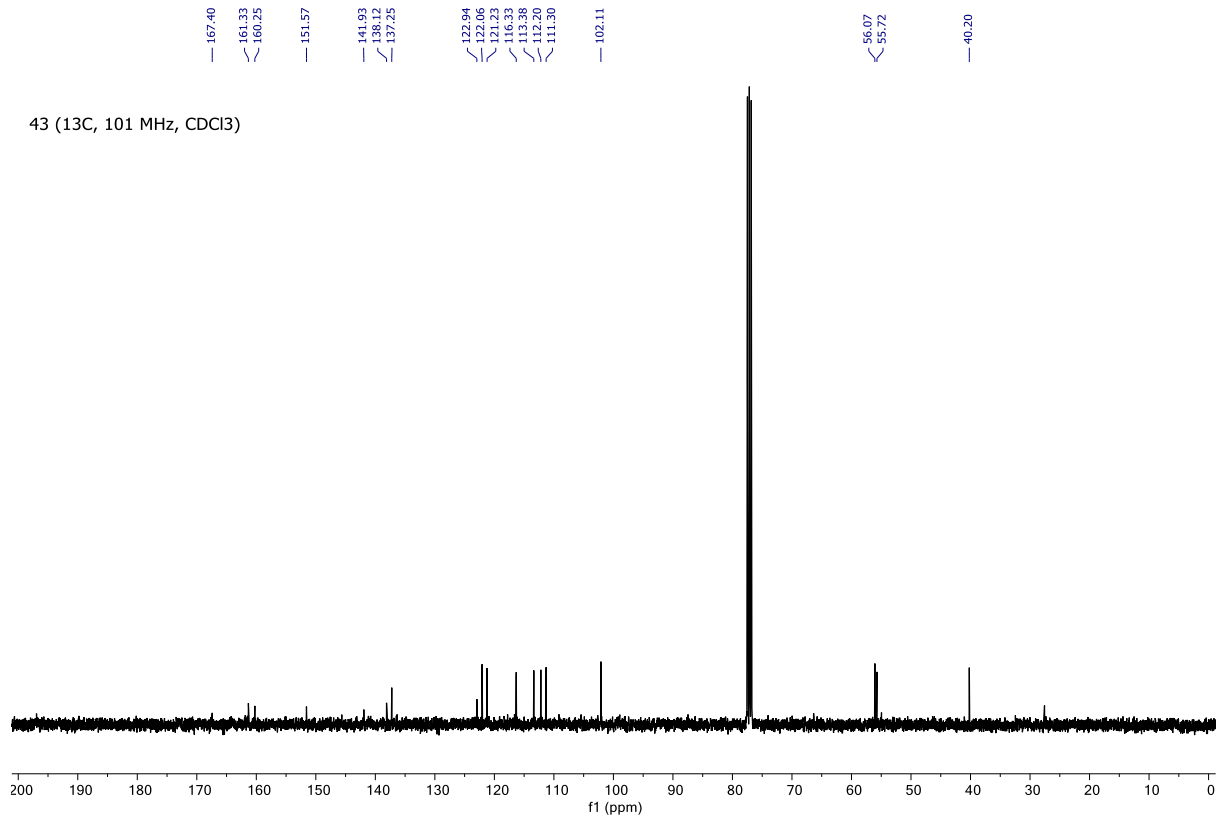
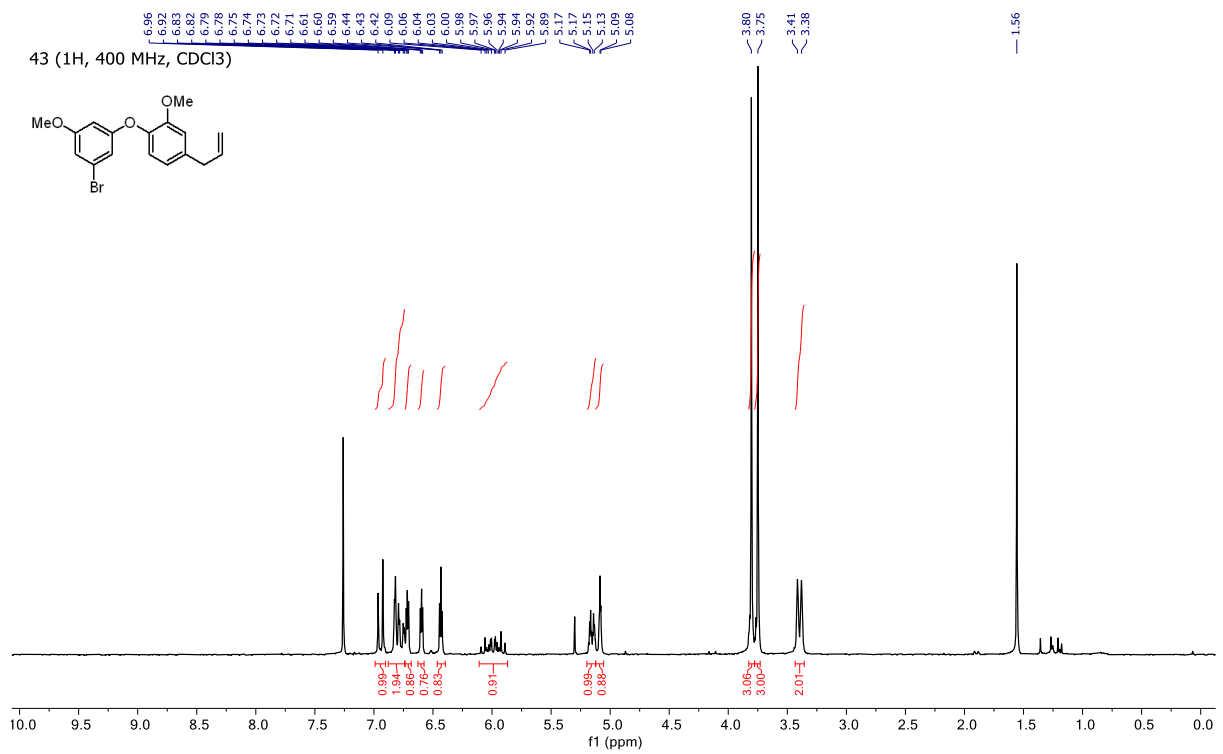


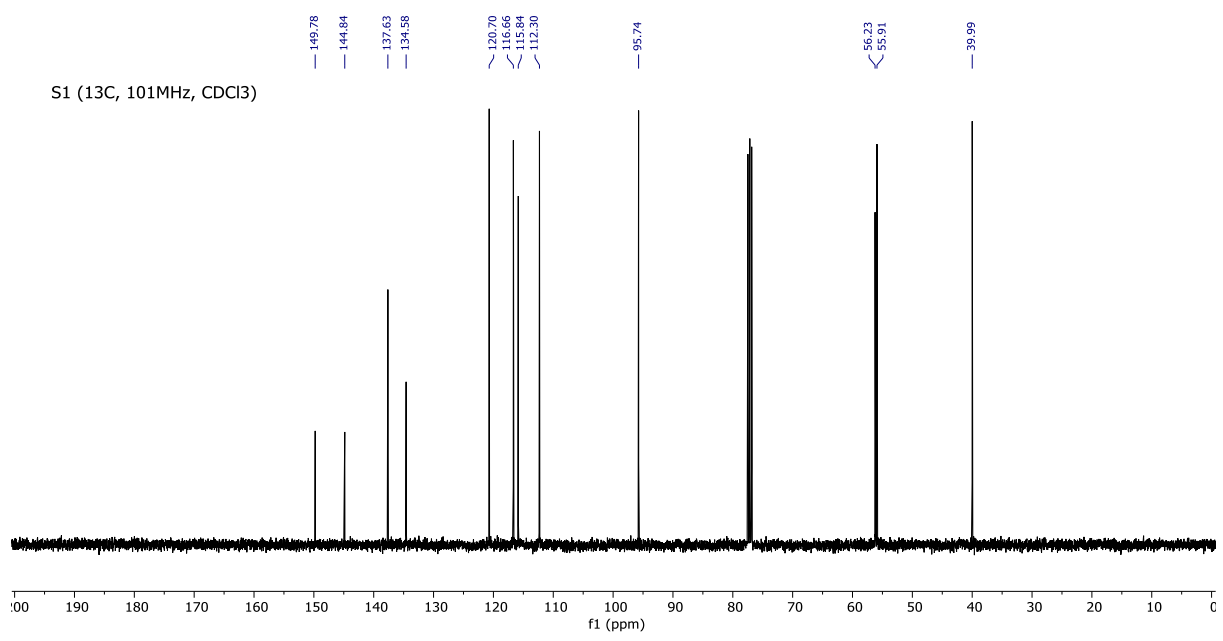
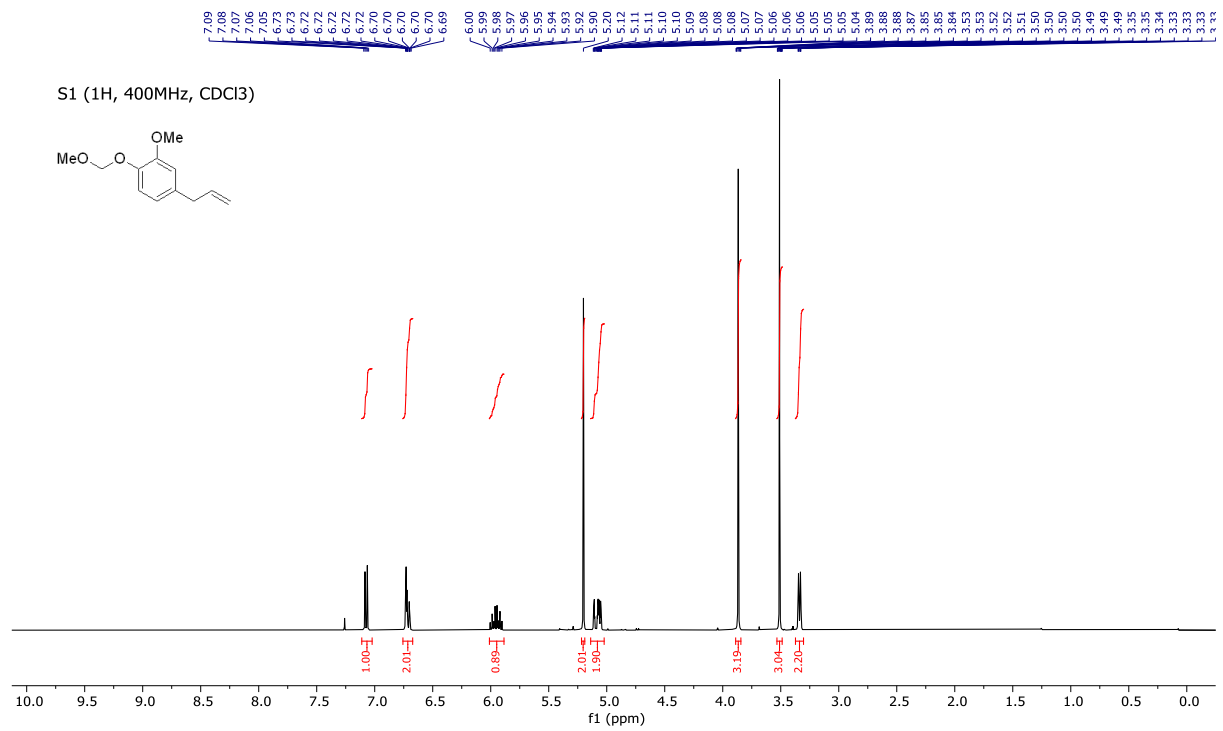


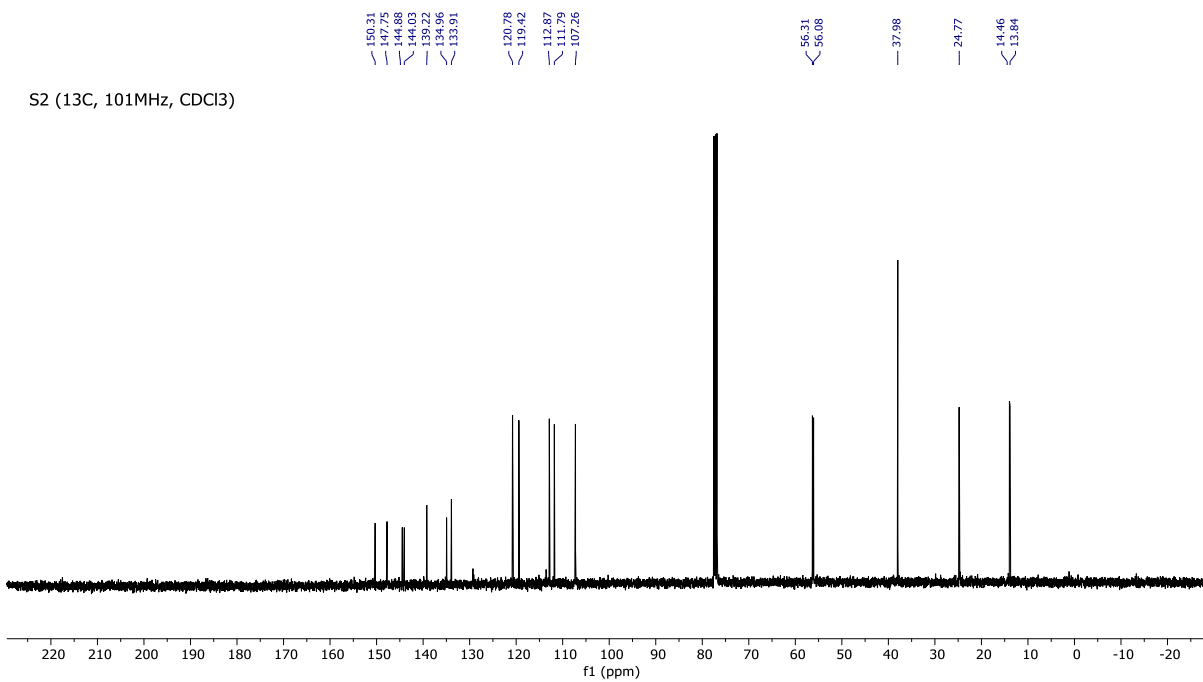
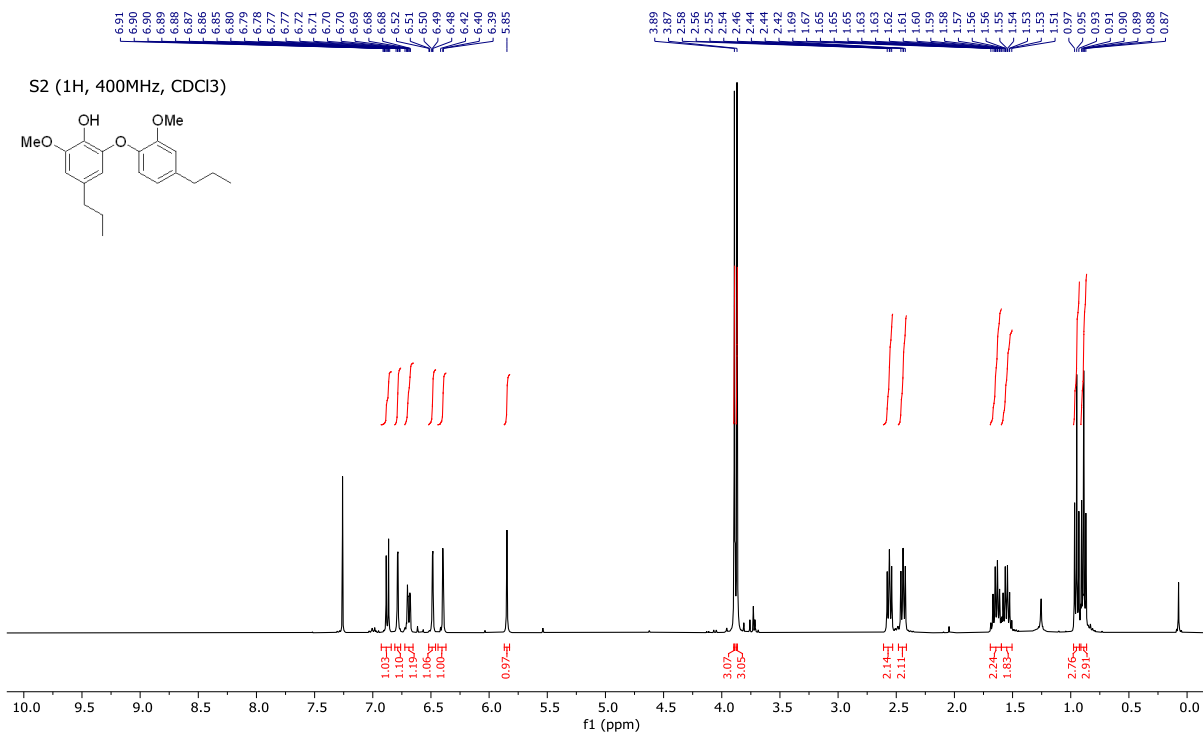


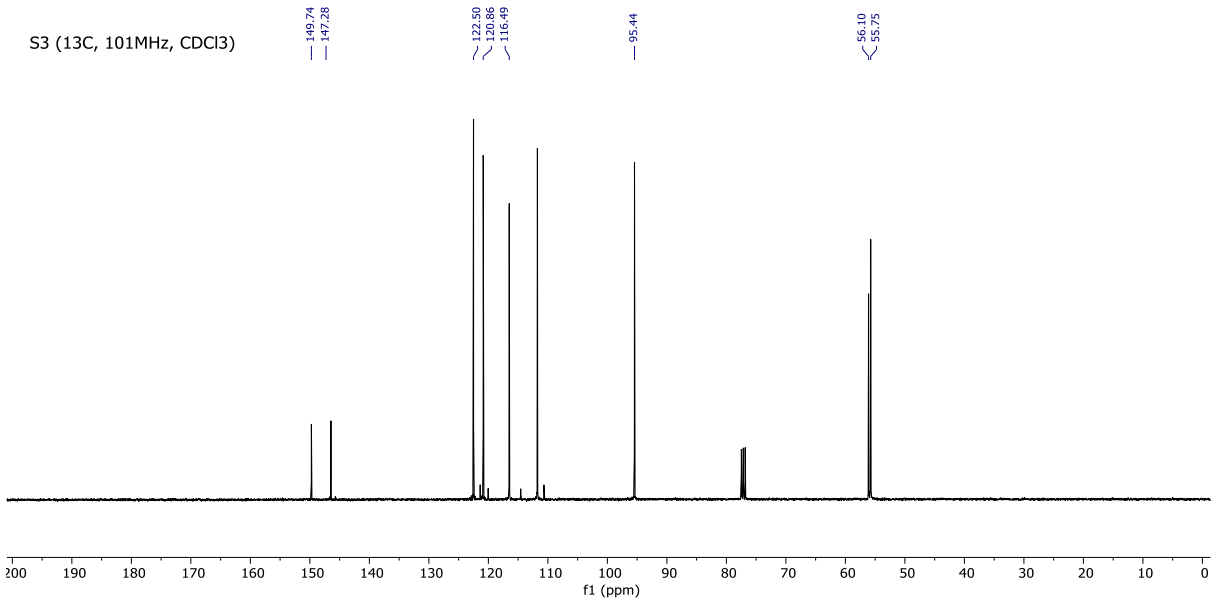
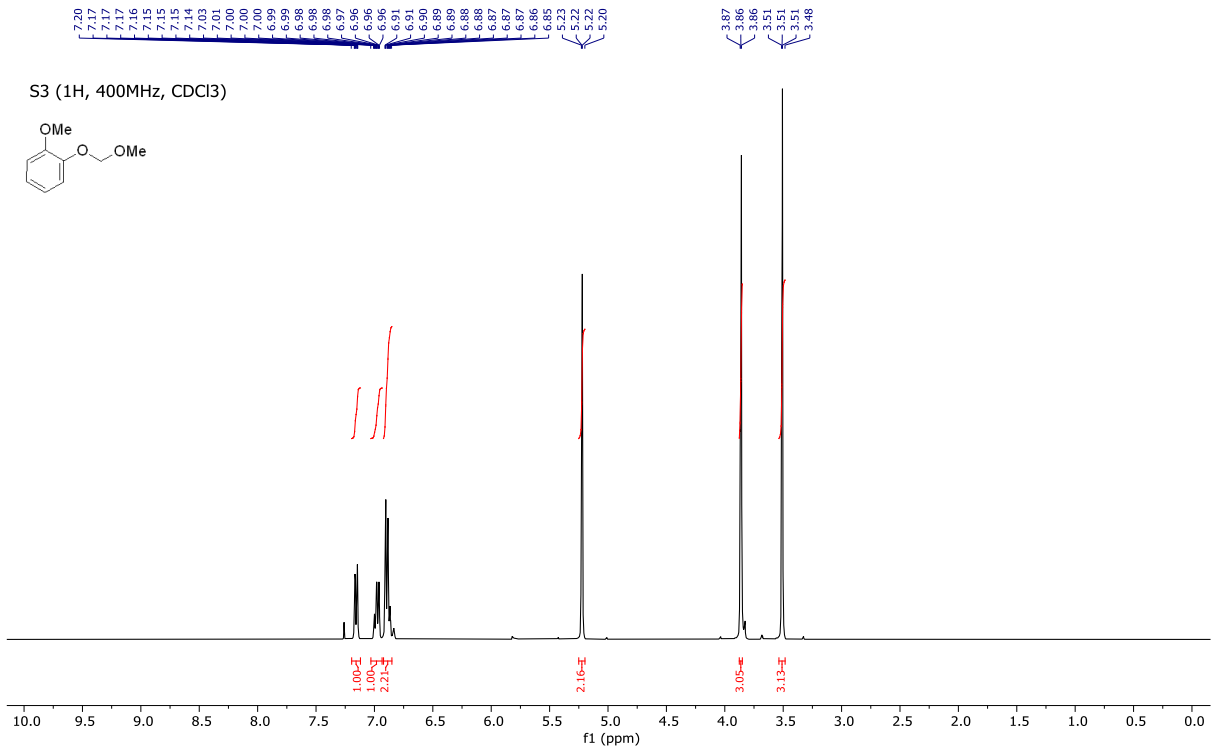




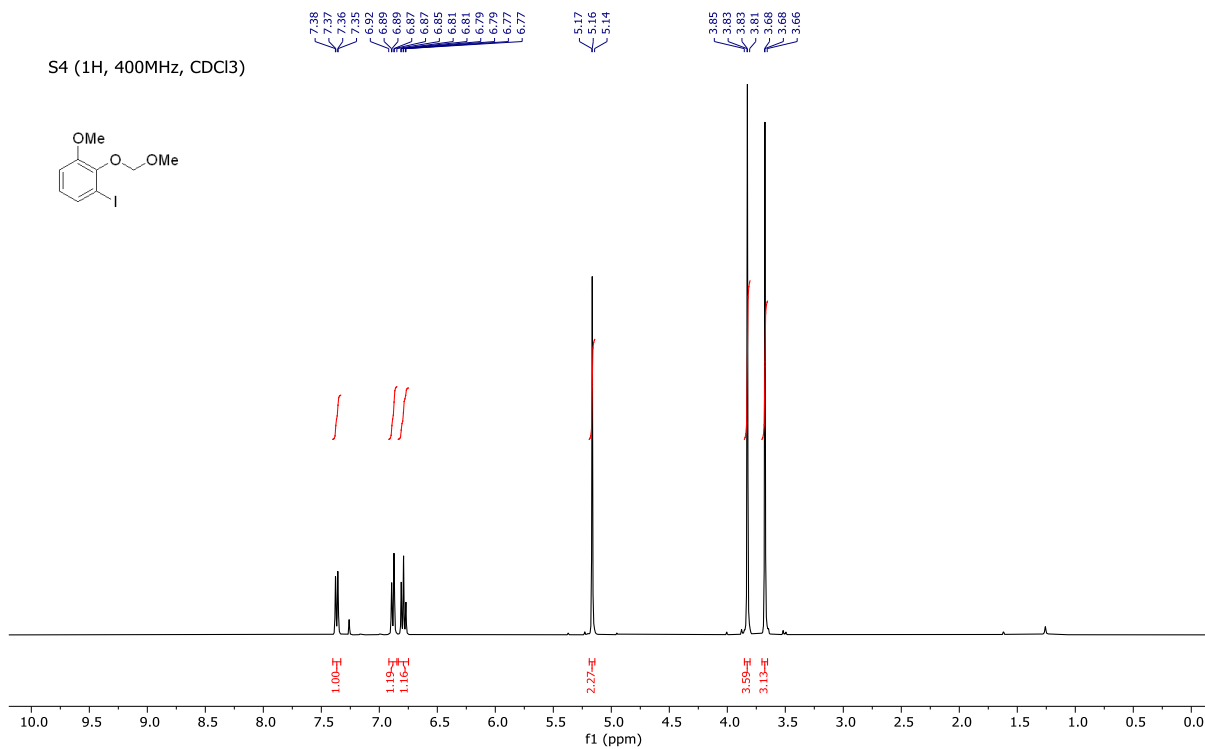
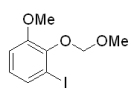




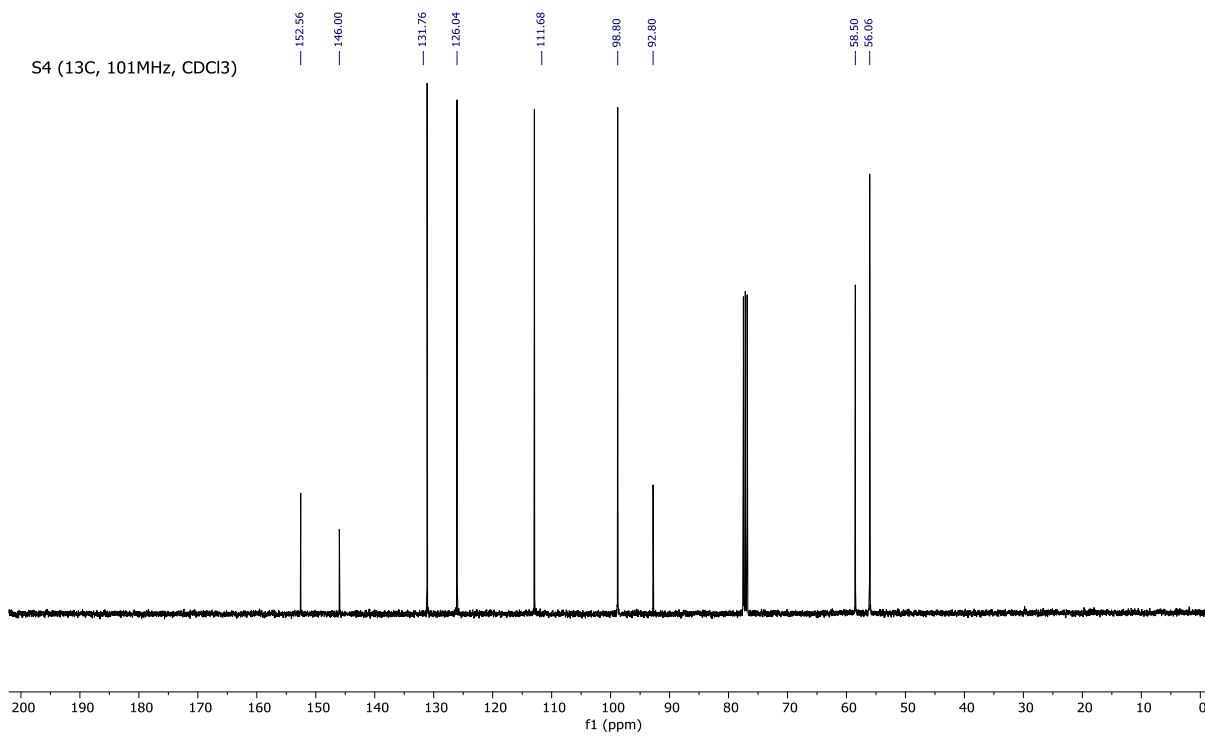


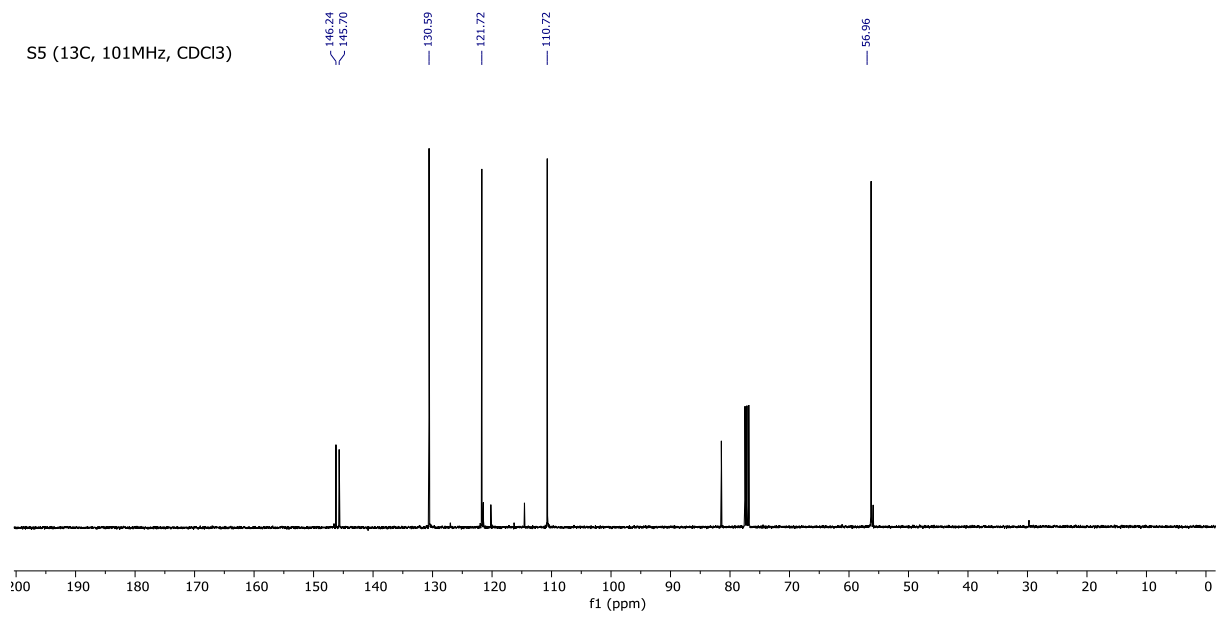
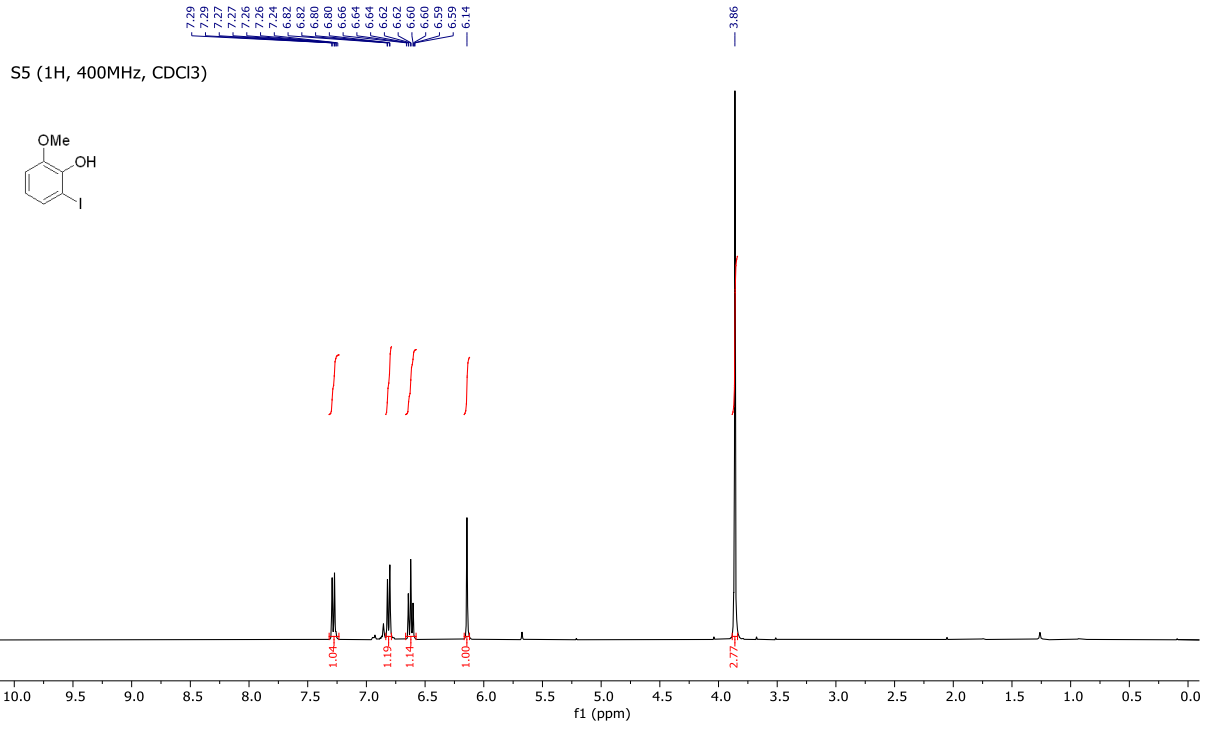


S4 (1H, 400MHz, CDCl3)

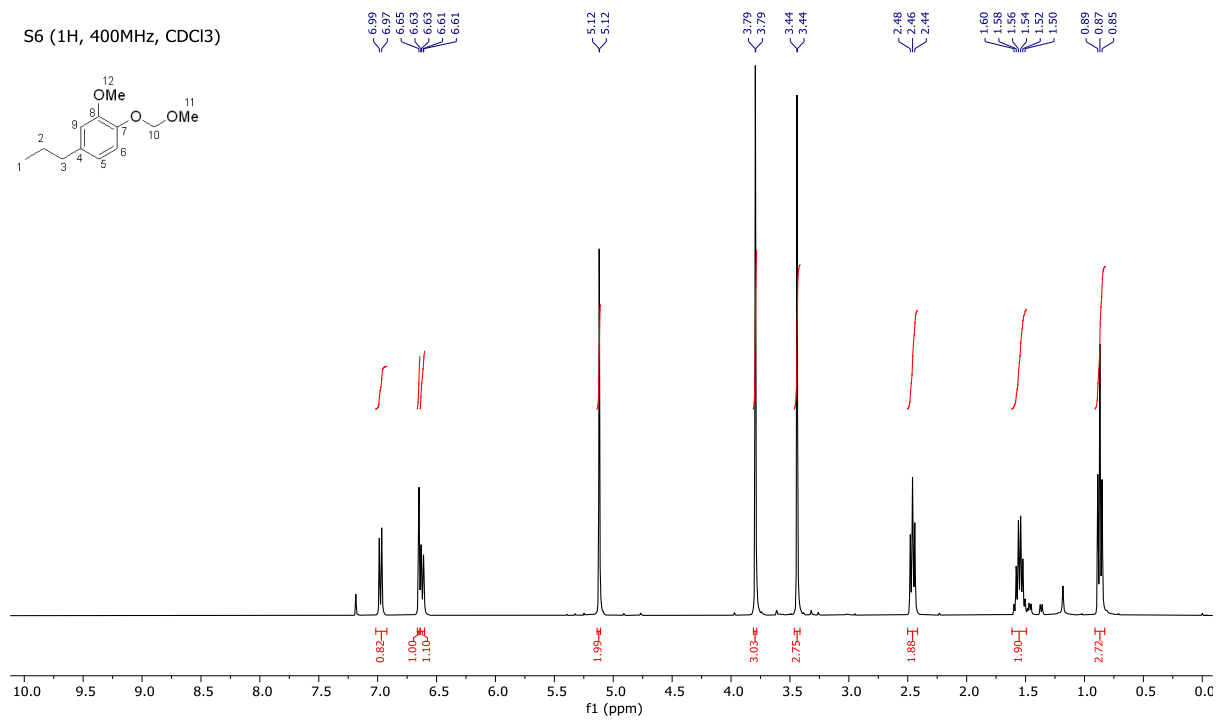
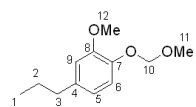


S4 (13C, 101MHz, CDCl3)

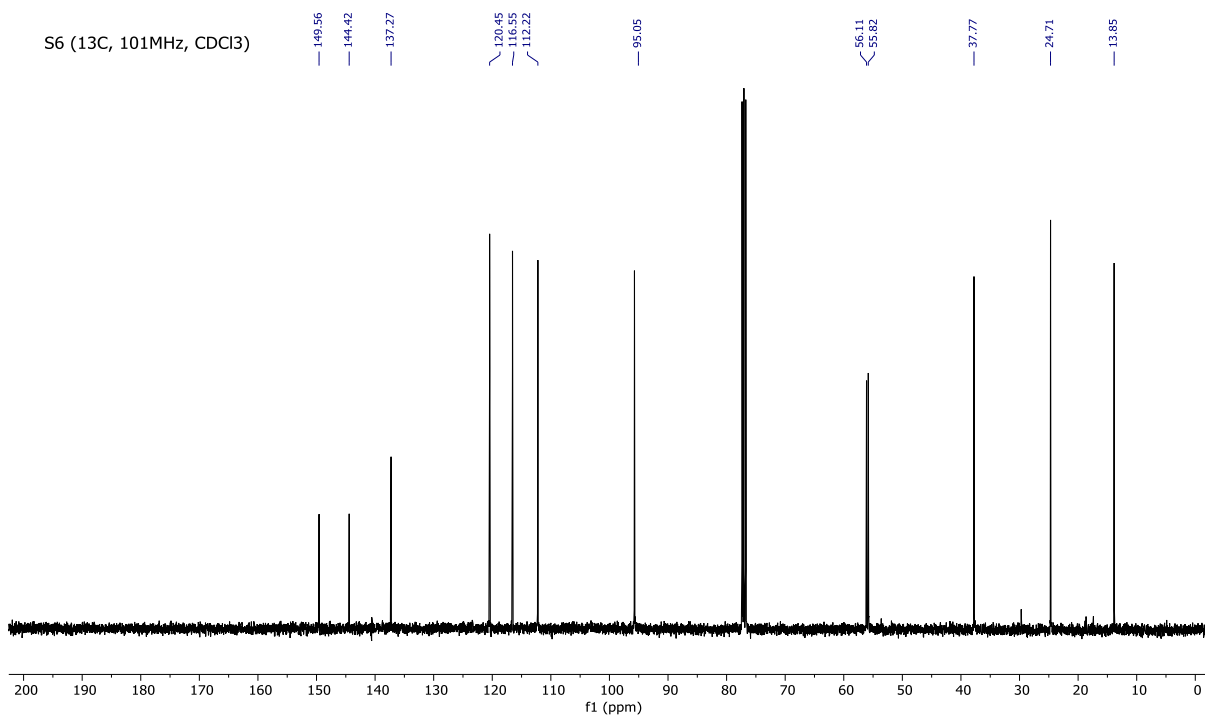




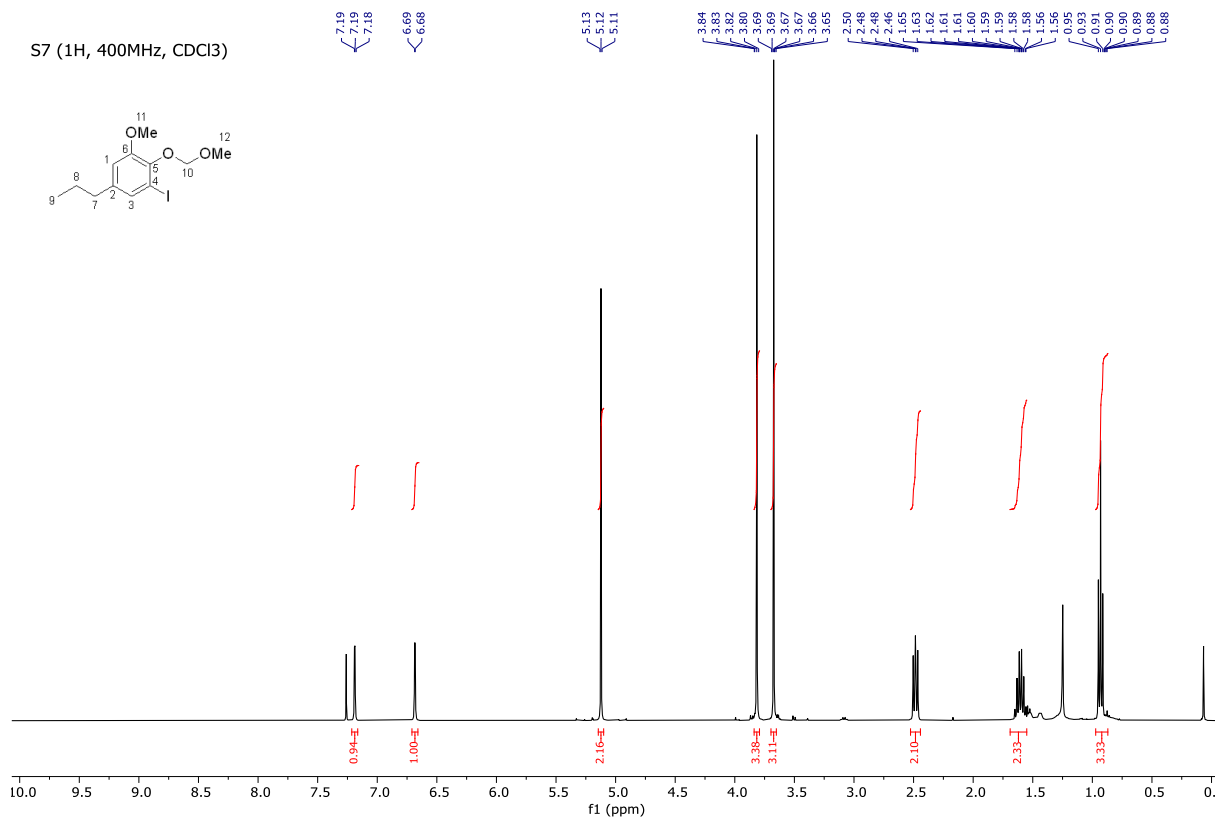
S6 (1H, 400MHz, CDCl3)



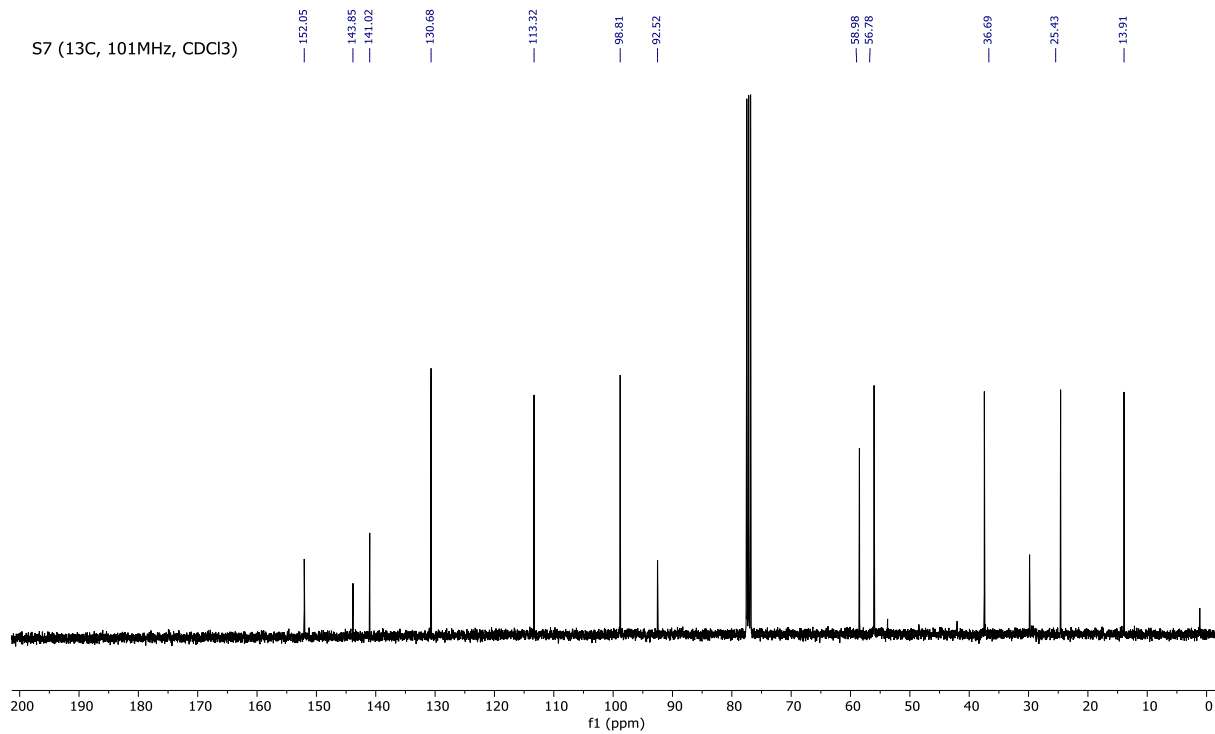
S6 (13C, 101MHz, CDCl3)



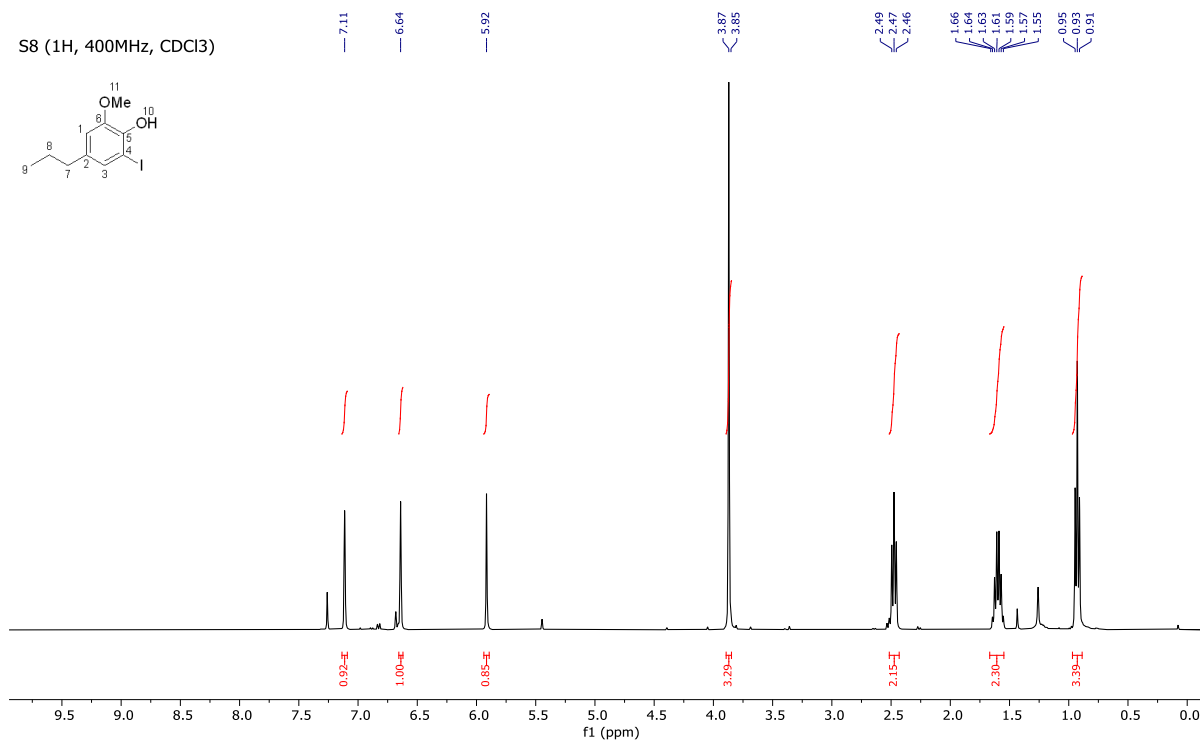
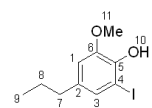
S7 (1H, 400MHz, CDCl3)



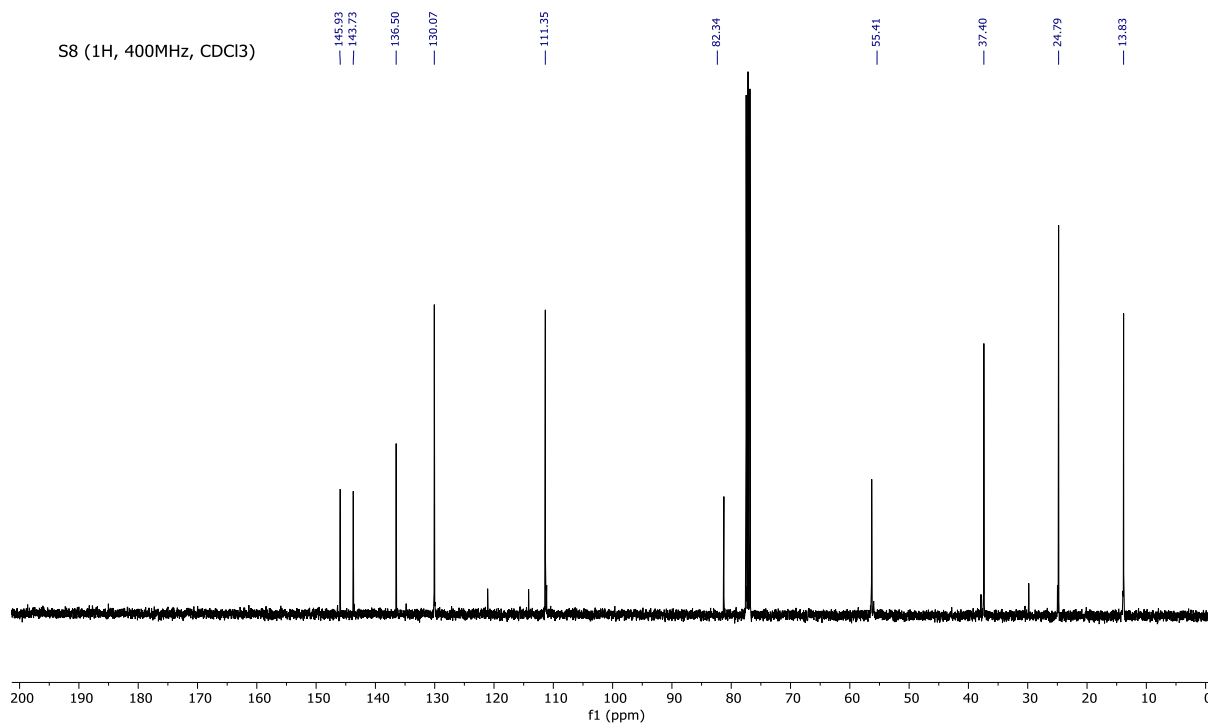
S7 (13C, 101MHz, CDCl3)

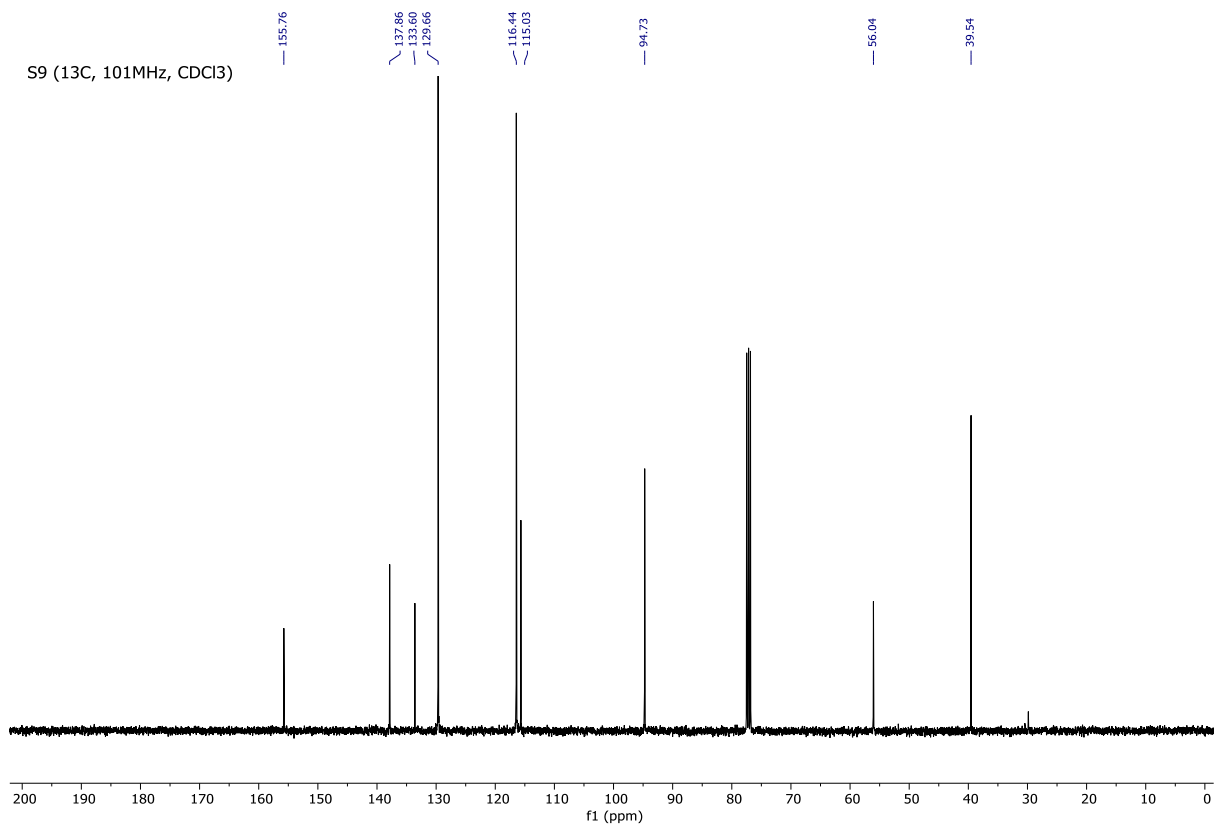
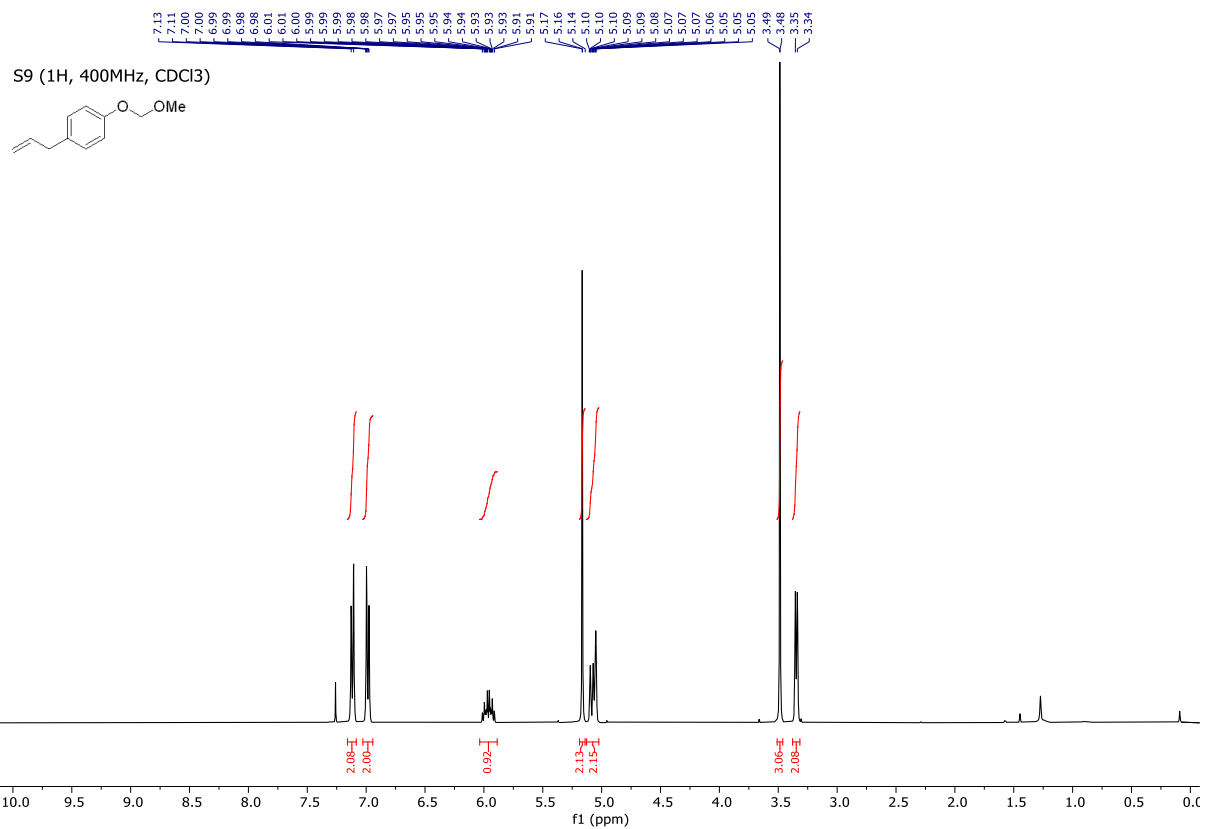


S8 (1H, 400MHz, CDCl3)



S8 (1H, 400MHz, CDCl3)





## 5. References

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